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ROYAL COMMISSION ON MATTERS OF HEALTH AND SAFETY ARISING FROM THE USE OF ASBESTOS IN ONTARIO

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180 Dundas Street
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VOLUME XXI A

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THE FURTHER PROCEEDINGS OF THIS INQUIRY RESUMED PURSUANT TO ADJOURNMENT

APPEARANCES AS HERETOFORE NOTED

DR. DUPRE: Mr. Laskin, are there any matters that you wish to raise before I greet the witness?

MR. LASKIN: I don't believe so, Mr. Chairman.

DR. DUPRE: Do your colleagues have any matters?

MR. LASKIN: Not this morning.

DR. DUPRE: Well, may I then, if you please, greet most warmly Dr. Paul Kotin. I was looking at the transcript of our last hearing at which Dr. Kotin appeared last February, and I noticed that I remarked at the time that I would not be at all surprised if Dr. Kotin was asked to respond positively to an invitation to appear as an expert in the formal phase of our hearings.

I congratulate myself on my forecasting ability. Dr. Kotin was asked and we are indeed grateful that he has responded positively.

So may I, Dr. Kotin, thank you for agreeing to come to give sworn testimony, and before I hand you over to Mr. Warren, who will conduct the examination, may I ask, please, Miss Kahn to swear in Dr. Kotin.

PAUL KOTIN, SWORN

EXAMINATION-IN-CHIEF BY MR. WARREN

DR. DUPRE: Mr. Warren, please.

MR. WARREN: Thank you.

MR. WARREN: Q. Dr. Kotin, we all know your present position is with Johns-Manville Corporation, but I thought we would begin this morning by taking the Commissioners back over your background so that everyone will understand where you come from and what kind of expertise you bring to the questions which we have been discussing in these hearings.

Following your graduation from medical school and your tenure in the armed services during World War II, and your private practice in California extended to 1948, you subsequently began your career as an academic pathologist. True?

THE WITNESS: A. Yes, sir.

Q. Can you tell us what you did in those early years? As I read from your curriculum vitae, you spent over ten years in the Los Angeles area as a practicing pathologist and as an academic pathologist with the University of Southern California.

Can you tell us in general what your dealings were during that period, what they consisted of, and what sort of research you were involved in?

A. My duties were the rather traditional three areas of academic activity. I did service at the Los Angeles County Hospital, which is a teaching institution, for the University of Southern California School of Medicine. I taught pathology to medical students both in the traditional course in pathology and a course in experimental pathology. Then I was engaged in research activities as well.

The research was oriented to the effects of, in this case, the chemical constituents in polluted urban air on the respiratory tract, both experimentally in terms of using animal

A. (cont'd.) model systems as well as clinically the study of patients, from the point of view of the pathologist, with histories of exposure to or clinical signs and symptoms of respiratory disease.

Q. The research then that you were engaged in in this period until 1962, focused, would it be fair to say, principally upon respiratory disease and questions involving the pathology and biology of the causation of respiratory disease?

A. Yes, with particular emphasis on neoplastic diseases - on cancer of the respiratory tract.

Q. That was my next question. When did you begin working on questions of carcinogenicity as related to respiratory function?

A. I would say at the very outset, since the response of the animal system to inhalants was a continuum. The end point that my associates and I chose was cancer, but a whole series of events take place in response to exposure to inhalants that are not cancer but in many instances are related to the ultimate evolution of cancer, and in some instances not. So it was a continuum. There was really no fine point...but the end point from the very beginning was cancer, and the support coming from the National Cancer Institute for our research rather indelibly emphasizes that our primary orientation was to cancer.

Q. Now, in 1962 you left the University of Southern California...maybe you didn't...yes, you did leave, or did you leave, maybe I should ask. When did you go to and start working with the National Institute of Health?

A. I believe it was in 1961 that I went. The official appointment may date from 1962, but in 1961 I was asked by the director of NIH, Dr. Shannon, and by the director of the National Cancer Institute, Dr. Endicott, if I would be interested in an appointment at the National Cancer Institute, in essentially

A. (cont'd.) the same area as I had been working in at University of Southern California, and that is the study of the causes and determinants of cancer, the natural history of cancer, and particularly with orientation to environmental causes and environmental determinants of cancer.

Q. Following your departure from Southern California in 1962, did you, during the decade of the sixties, essentially cease teaching responsibilities and become a researcher?

A. No. Actually during the course of my ten years at NIH, five of them in the Cancer Institute and five at the National Institute of Environmental Health Sciences, I maintained an academic appointment throughout this period, and it was essentially more than just a catalogue appointment. I had fixed teaching responsibilities when I was in the Washington area, at the University of Maryland School of Medicine, and when I was in North Carolina at NIEHS, I had a joint appointment as Professor of Pathology at Duke University School of Medicine, and at the Univeristy of North Carolina School of Medicine, and essentially pretty much had the teaching of the pathology of neoplastic diseases at both institutions as my responsibility, in the sophomore course in pathology.

Q. During the entire period with first the National Cancer Institute and then in NIEHS, you conducted a considerable amount of research on the issues which we have been discussing, I take it?

A. I think it would be fair to say that I was involved with a considerable amount of research...I guess ultimately responsible.

The actual type of research that I did at the University of Southern California, which consisted of everything from filling water bottles and cleaning cages to ultimately doing the pathology on the models that we used, was pretty much delegated in the sense of day-to-day activities. In terms of

A. (cont'd.) the overall responsibility for the experimental activities, I did have an involvement. I was involved in protocol design, I was involved in rationale for doing certain activities, I was involved in the ultimate diagnoses using pathological techniques, and most particularly was involved with attempting to make some sense out of what we did and saw over the period of the experiments.

Q. What I would like to do this morning is to call upon your experience in biology and pathology and physiology and teaching to give us maybe our first lesson in pathology and biology 101. Put aside that discipline of epidemiology and try to turn to biology per se and see what we can learn.

The first issue that I would like for us to discuss is how do fibers, asbestos fibers, or particles in general, get into the body? I thought for all of us to discuss this question it might be useful to turn to your article at tab three, figure one on page 135.

Now, this is a simple schematic diagram of the respiratory tract, and I would like to ask you a number of questions about what type of fibers, what length of fibers, what diameter of fibers, get into the respiratory tract and where they are likely to be deposited.

First of all, in terms of the entry and deposition of fibers in the respiratory system, is diameter or length of fiber the key determinant of deposition?

A. Diameter clearly has the greater influence on deposition than length.

Q. Can you explain to us why that is?

A. Yes, I can tell you what is observed. I don't think anybody can really explain it.

When we inhale fibers, for a fiber to get from the external respiratory environment down into the lungs, it has to go through a very tortuous path through the nose, through

A. (cont'd.) the accessory nasal sinuses, the nasal pharynx, and so on, and each in conformity with the physics of particle flow, the principles of rheology, the science of flow, and so on, these particles are able to penetrate the respiratory tract on the basis of size.

In the instance of an aerosol particle, which could be a sphere, let us say, there the diameter is virtually the exclusive determinant.

In the case of fibers, and arbitrarily a fiber is defined as a material that has a greater than three-to-one aspect ratio , length to diameter, the length can very significantly interfere with inhalation just mechanically through the upper respiratory tract. But nevertheless, the diameter equally and perhaps more importantly can interfere with...or determine penetration.

A rule of thumb with the standard deviations that would go with any biological phenomenon it's generally believed that a fiber thicker...with a greater diameter than five micrometers, will not penetrate the upper respiratory tract to get down into the trachea, the windpipe and then into the arborizations of the tracheobronchial tree.

But once a fiber gets down into the trachea, independent of its length...and fibers have been recovered from the lung up to two hundred micrometers in length...independent of its length, its diameter, both in terms of the depth of penetration and its sedimentation rate.

There you find that deposition will take place within the tracheobronchial tree in conformity with some broad dimensional boundaries. One can say that the larger the diameter of the fiber, the more...the higher in the trachobronchial tree, the closer to the trachea, that it will be deposited.

Q. Let me go back over some things that you said and see if I understand this from the simplest and most

Q. (cont'd.) elementary standpoint.

I envision that when I breathe in a room with a cloud of fiber dust that I breathe in, I inspire, and the fibers go into my nose and down this tract, which is schematically presented in figure one. I envision it kind of as a particle in a wind tunnel, or something like that. It's being buffeted about by all kinds of forces which, in a complex way, determine whether or not it's ever going to be deposited on the walls of that tunnel. Is that a fair, simple-minded way of looking at what is going on?

A. It's fair except for one thing, and that is a wind tunnel, I think, carries with it a definition of a continuous nonbranching type of system. Whereas in the trachea and the bronchii, the windpipe and the bronchial tubes, you have branching exactly like a tree, really. So you have opportunities for mechanical impingement as the particle comes down this wind tunnel, which we can say that the wind pipe, the trachea, represents. It immediately hits the first branching area and indeed some of the particles will just mechanically be forced against this focus of branching, and then if you can...this is repeated many, many times throughout the bronchial tree.

So if you accept that, then it's like the wind tunnel.

Q. Okay.

DR. UFFEN: Is it important the reversing, you breathe in and out?

MR. WARREN: Yes. I want to get to that too, and I will get to that, I promise.

DR. UFFEN: I'll wait.

MR. WARREN: If I don't do it right, you could certainly correct me.

MR. WARREN: Q. I envision it then, that there are various kinds of forces which are affecting the deposition of particles in the trachea, the pleura, the lungs and so forth...

THE WITNESS: A. Just for the record, particles do not settle out on the pleura.

Q. Okay. One of those is gravity, I take it? Simply a particle has some weight and it can...like any other particle, it has a tendency to fall?

A. There is a sedimentation rate for particles, exactly. It is related to the physical properties of a particle. Yes, sir.

Q. Then I guess there is a second one which you have been suggesting, and that is that we don't have a straight wind tunnel, we have a lot of detours, and the particles naturally bombard or bang into these irregular wind tunnels. So sometimes particles can get...can adhere as a result of that kind of bombardment?

A. Yes, or impingement can occur as a result of this bombardment.

Q. What other kinds of forces, from the standpoint of physics, are at issue here in determining rates of deposition?

A. Well, there is the depth and force of the inspiratory effort that is also a factor - how deeply you breathe, how forcefully you breathe. The head of pressure, as it were, behind the breath that you take, is another factor. Less important. but nevertheless a factor.

Q. Okay. Now, let's take Dr. Uffen's question for a second. My simple-minded schematic view of what is happening is, we have this wind tunnel and fibers are coming in, but Dr. Uffen suggests that I breathe in, but also breathe out, so there is going to be a reverse force occurring there. What is the significance of that?

A. Well, the reverse force, again, is muscle-controlled in the sense of the movement of the diaphragm and to a lesser degree, the muscles between the ribs and the rib cage.

A. (cont'd.) But as you expire, the particle content of the expired air is understandably less. First of all, the material that has settled out is not part of the expired air.

But again, I think there are dimensions of particles which, because of their size, never settle out and remain suspended in the tidal air, and they just go in and out.

But basically, it is a different air that is exhaled from the point of view of particulate content.

Q. So the inhalation/exhalation, inhaling and exhaling aspect of it means that we inhale a quantity of X and we exhale a quantity of Y, and the difference is the potential for being deposited in the system? Fair enough?

A. For particulates? Yes, sir.

Q. Now, let's talk about particle size in relation to these physical phenomena that we have been talking about. Why is it, first of all, that fibers...I think you said of greater than two hundred microns in length...aren't going to get into the system?

A. Well, depending upon diameter, an occasional one will. But the upper repiratory tract is a very efficient filtering system, and these large-size fibers...and again with diameter as the main determinant...that are too large to get by, just mechanically, the filtration that is associated with the upper respiratory tract, will be trapped and be removed either mechanically or passively. So it's...you really can't put a quart in a pint bottle, is what the situation is there.

If we envision a particle, let us say that is a hundred to two hundred micrometers in length, but it is perhaps three or two micrometers in diamter, it will be handled aerodynamically on the basis of its diameter. In fact the sedimentation rates will be equivalent...the force will the square of the diameter.

So that having got through the upper initial

A. (cont'd.) hurdles of getting into the respiratory tract, then the fibers will settle out, and again with physical laws which we have no concept of in terms of their evolution...I don't understand the physics behind it...will settle out with the larger particles settling out more centrally, the intermediate particles settling out in the intermediate branches of the tracheobronchial tree, the very smaller particles will settle out in the distal branchings of the tracheobronchial tree, and then there are particles, as I said earlier, of some size which are sufficiently small, tiny, that they really don't get suspended but remain...don't get deposited, but remain suspended in tidal air, and they are inhaled and exhaled and in animal models you can demonstrate this by...presently, you can use radioactive materials, but in the old days before that we used to use fluorescent aerosols so we could measure the settling of particles by capitalizing on the fluorescence of the particles.

Q. Okay. Let me go back over this and see if I understand it.

When we are talking about fibers greater than two hundred microns in length, by and large, with the rare exception, those fibers don't get into the system simply because they are too long and they can't enter, as you said, it's like a quart in a pint bottle?

A. Unless the diameter is such that it can get its way through, but this is not a common phenomena.

Q. Then it's fair to say thereafter, once the fiber gets into the nose and into the trachea, the key determinant becomes diameter because that is the variable which affects most significantly the sedimentation rate?

A. That's correct, yes.

Q. Now, what do we know about sedimentation rates and deposition by fiber diameter as it relates to deposition in the various organs of the respiratory tract schematically presented

Q. (cont'd.) in this figure one? Can you give us sort of a cutoff diameter, and so forth?

A. Yes, but I would caution that the standard air in the numbers is very, very great. But nevertheless, one would say that particles with diameters...the largest diameters that are able to get through the upper respiratory tract...down to perhaps three to four micrometers, will impinge early, or high up on the trachobronchial tree, and then will sediment down perhaps to the level of between the secondary bronchii and the segmental bronchii, and these are just names for the successively smaller arborizations of the trachobronchial tree.

Q. Can you show us...can you point to or show me on this diagram where those are?

A. I would say it would be just about where the crosshatching in the right lung stops. You notice that I have a circle which is used for a blowup below, but immediately within the circle the crosshatching of the bronchial tree, which is cartilage...it's meant to represent cartilage...stops, cartilage that surrounds the bronchii.

But it would be somewhere down...two-thirds of the way. That would be about it.

Q. So where that hatching stops within the circle is roughly what we are talking about here?

A. Yes. Perhaps a little farther down - two-thirds of the way as I look down, I think.

Q. Now that means that it's between the nose and that point where virtually all of our fibers with a fiber dimension greater than three or four have sedimented out?

A. It's where, if only the laws of dynamics and kinetics of settling were the exclusive factor, that would be where most of them settle out. Yes, sir.

Q. In saying that most of the fibers, let's say... I'll take a number...three point five or four, I don't really care...

Q. (cont'd.) most of the fibers with a diameter greater than, let's say three point five, settle out before that point. Do we have animal experimentation, or human experimentation for that matter, which demonstrates that as a real-life fact the laws of physics are operating in this way?

A. Yes. With a wide variety of agents perhaps, the amount of work done with asbestos in these forms of mechanism studies and so on have been rather considerably less than with particles of other types. But by and large, there is a consistency between the handling of particles or various chemical types, as long as the dimensions are constant from material to material and from species to species. There is very little interspecies difference in the handling of particles.

Q. Let's detour on that point just for a minute. Again, I'm approaching this from a common sense rather than an experienced medical standpoint.

I envision that I'm a person over six feet tall, you know, a big person, as opposed to a mouse which has very, very much different dimensions and very much different anatomy, and very much different systems in every sense of the word.

How do we know, or why is it fair to be able to generalize these kinds of phenomena from rodents or other species to man?

A. Well, this is something that has been known for a long time - well over a half century - dating back to the time when infectious disease was the primary cause of illness, and animal models were used to study the distribution of infectious diseases that infected animal systems, including man.

The term that was used, that we can use to measure the distance between the nose where we would inhale something or where an experimentalist might put a drop of fluid containing the virus of a pneumonia bacillus or a pneumonia coccus or something like that, the snout-carina distance.

A. (cont'd.) The carina is, if you'll go back to the picture, the area where the first bifurcation or the first splitting of the trachea.

The snout-carina difference, the experimentalists learned in the early twenties, really had very, very little influence in how rapidly a suspension of micro-organisms would traverse that upper part of the respiratory tract, so as paradoxical as it sounds, the snout-carina distance of a steer and the snout-carina distance of a mouse, while orders of magnitude different, did not affect the ultimate distribution and dissemination of a particle through the lung.

Do you follow me? That once it got down into the lower respiratory tract, the area it traversed to get there was not a major determinant. This is why there is a great validity for rodent models in many, many areas of experimentation, why the data have some relevance to man.

Q. Let's talk about below the point that we cut off. We've got your diagram here and we have a circle, and at some point two-thirds of the way down there, we stop seeing, as a general rule, fibers with diameters let's say greater than three point five microns. What can we say about the fiber diameters of those fibers which are deposited below that point?

A. Again, the studies with asbestos fibers are... well, let me first say that the major knowledge we have of the deposition of fibers are not with kinetic studies which determine where the fiber is during the course of the experimentation. What most of the data address themselves to are on studies where after the exposure has taken place and the animal has been sacrificed, then, as it were, the lung is segmented and a distribution pattern is made of the fibers at the various levels of the lung.

Do I make myself clear?

Q. Mmm-hmm.

A. Well, obviously that isn't nearly as satisfactory as measuring it as it goes in, as can be done, as has been done, with other materials. But one can say that using this technique... and I just mention it to emphasize some of its limitations...that when one gets down to beyond what I refer to as the segmental bronchii, and gets down into the area of the branching tree that we refer to as the bronchioles, which is just a polysyllabic word meaning smaller bronchii, I guess, the particle diameters will get down from the three and a half, which again is a figure that I say with some trepidation, down to one micrometer in diameter, and that will fall into that area of the tracheobronchial tree.

Then distal to that, when you get from the bronchioles down into the actual air exchange area of the lung, the alveoli, the air spaces, and the alveolar ducts...which are tubes, as it were, that connect the bronchioles to the air spaces, you are then dealing with particles with a diameter of micrometers or less.

Q. Let me see if I understand this. Does that mean then that we could draw another line which would say that between the point where I previously drew the line and down to these alveolar sacs which are displayed in the kind of blowup circle, we are talking about fibers from say one to three and a half microns in diameter?

A. Yes. I'm a little uncomfortable with the numbers, because...

Q. Sure.

A. But as an approximation, accepting all the caveats, yes.

Q. Yes. Then it is those, again recognizing that we are talking about a generality here which doesn't apply to every fiber, when we get to the alveolar sacs themselves, then we are talking about fibers of less than a micron in diameter?

A. A micron in diamter or less, yes.

Q. Something that you said earlier is probably worth talking about for a minute. You suggested that there might be some fibers which are so fine, short, thin or maybe both, that they simply remain suspended permanently or never are deposited. Can you give us some sense of what kind of fibers we are talking about?

A. Yes. There we are dealing with fibers that are measurable in perhaps hundredths to thousandths of a micrometer, millimicrometers. That would be the unit of measurement.

They, as you said, just remain suspended in tidal air. They can settle out by just the fortuitousness of their bumping in, bombarding, as you said, the impingement on any one of these branching areas, but basically in terms of the laws of ...the physical laws of settling, they can remain suspended, and in fact do.

Q. So at some point the forces of gravity or sedimentation are such that the fiber can stay essentially airborne at a very, very small dimension of size?

A. Yes. An analogy would be the stream of sunlight that comes alongside the curtain that you have drawn and you see the dust particles engaged in Brownian movement. They are there, they move, they are not static, but they don't settle out.

It's, I suppose, a poor, but nevertheless a visual analogy and no matter how much you walk by or may walk through that column of dust, that's visible by virtue of this Tyndall effect, why it just stays in the air.

Q. Is the Brownian movement just the summation of all the forces that are acting on the particles that are in a suspended state like that?

A. Brownian movement is the movement associated with...on the basis of the physical characteristics of particles in relation to one another, and in relation to the medium in which they are suspended.

Q. Having explored deposition of particles throughout the system here, can you tell me what sorts of clearance mechanisms may operate to eliminate fibers which have been deposited throughout any place in this system?

DR. UFFEN: Counsel, before you leave deposition, can I ask a question?

MR. WARREN: Sure. Go right ahead.

DR. UFFEN: To what extent, sir, is it necessary to consider whether it is laminar flow or turbulent flow?

THE WITNESS: It's terribly, terribly important, as I'm sure you are aware, because one can show that around each bifurcation there are eddies of air, and this is very beautifully reflected in what the pathologist sees through the microscope, because the first area a pathologist is going to see any changes in animals or in man that are exposed to inhalants, is in there areas immediately adjacent to and part of these successive branchings.

Exactly. The turbulence there causes a deposition which is immune or separate from the orderly flow that we have been talking about this morning, and one sees that one of the...I guess one of the generalizations is if you are going to look for abnormalities in the branchings of the tracheobronchial tree associated with inhalants, the first place to look is at these areas of branching, at the apex of the pyramid of this little branching area, as it were, and immediately around it.

DR. UFFEN: When you breathe in, it's one thing, and when you breathe out it's flowing the other way. Are these both turbulent, inhaling and exhaling?

THE WITNESS: I really don't know. I would suspect that there would be less turbulence, just on the basis of the force behind the column of air, on exhalation. But I am unaware of that, sir.

DR. UFFEN: Thank you.

MR. WARREN: Q. We have talked about sedimentation rates and deposits. Let's take fibers which are deposited and can you tell us what sorts of mechanisms there are in the lung to clear out those deposited fibers?

THE WITNESS: A. Well, there are essentially two mechanisms. One relates to the actual anatomical structure of the branches of the tracheobronchial tree, and beginning with the trachea and extending down just proximal to the bronchioles, the lining of the cells, or the lining of the bore, as it were, of the tracheobronchial tree, consists of several types of cells, but two that are relevant to your question.

One is a cell that has the capability of secreting mucous, synthesizing mucous within the cell, and then excreting the mucous into the lumenal surface of the cell. This mucous is constantly being secreted, it's a mucous that is rich in mucous materials that allow it to diffuse over the lining of the tracheobronchial tree and form a blanket, as it were, a mechanical barrier. This mechanical barrier does not have a static residence, but is propelled by the second of the two types of cells that I was referring to, and these cells are referred to as ciliated cells.

These are cells that have little brush borders. They have little whiplike, hairlike brads which extend from the lumenal surface of the cell into the bore of the tube and they beat constantly, and they beat at a very, very rapid rate. One can visualize the beating with stroboscopic light where you can actually see the cilia beat, and it is a beat that is directed towards the throat. It is the motive force for this mucous blanket which we can now refer to as a mucous escalator, and the analogy to an escalator is a very, very precise one.

It goes in one direction and moves the mucous as well as the particles that are settled out on the mucous.

Q. Let's stick with this one for a minute then.

Q. (cont'd.) What you have been talking about is displayed, I guess, in figure one, once again, that we have been talking about. That circle there displays the airway, the mucous banket, the ciliated cells, and this is what we have been talking about?

A. Yes, sir.

Q. Now, if I envision a particle coming to rest in the trachea or the bronchial tubes, I am envisioning that that particle lands on the mucous blanket and you are suggesting that the cilia underneath that blanket propel it in one direction, and that is up to the throat?

A. Yes, sir.

Q. Suppose that that's what happens and I breathe in and a number of fibers land on the mucous blanket and are propelled up, what happens once they are propelled up?

A. Well, for the most part the mucous enters the throat and is unconsciously swallowed. By unconsciously I mean just passively swallowed.

If, indeed, for a variety of reasons the production of mucous in response to whatever it might be, an infection or an irritant or something, is greater and/or is symptom-producing, you have a conscious effort to remove that accumulated mucuous even while it's on the tracheobronchial tree, let alone when it gets up to the throat and makes its presence known, and then you cough or make conscious efforts to remove it, and you do it by expectorating.

Q. Does the inhalation of dust or fibers, whatever, cause the cells to generate more mucous than when there is less dust being inhaled?

A. This depends on both the chemistry as well as the physics of the particle, but yes, certain things can cause enormous amounts of mucous, amounts greater than normal to be

A. (cont'd.) produced and one sees this clinically in a variety of settings...cigarette smoking perhaps being the most notable one.

Q. We have talked about the first of the two defence mechanisms that you started to address. Before we go to the second one, where does this first defence mechanism the mucous ciliary escalator, cut off? I mean, physically, I take it, there are not ciliated cells and mucous at some point on this schematic diagram. Could you tell me where that is?

A. Well, certainly in the blownup circle on the left, which has bronchiole and alveolar sacs, that is at a level which has no mucociliary apparatus, and even more proximal to that, but still at the bronchiolar level, as it were. So it's at the bronchii and in the small bronchii, the segmental bronchii, that you begin to get a waning and disappearance of the mucociliary apparatus.

Q. So you would have mucociliary apparatus in the bronchial tubes, but it begins to feather out after that point?

A. Yes, sir. In the bronchioles.

Q. I guess like every one of the phenomena we have been talking about today, it's not like turning off a light switch or turning it on, it's a matter of degree? True?

A. The function of mucociliary...?

Q. Well, both the function and its existence. In other words, we don't have a point where we have full mucous ciliary apparatus and then, you know, one micrometer further down, none at all?

A. It's rather precise. It will vary all over, but the cutoff point is a rather precise one, yes.

Q. Now, let's talk about the second of the clearance mechanisms which you alluded to earlier. Can you tell us what that is?

A. That is a cellular defence capability, as distinguished from a tissue defence capability, and this relies on the ability of certain cells, cells that have, I guess teleologically speaking, the responsibility for the defence of the host against all alien materials or against alien materials, and these cells produce their effect by their ability to engulf foreign agents. It can be a micro-organism as well as a chemical agent, some substance which would produce this effect by virtue of its physical properties.

In engulfing this, it sort of sequesters it from the rest of the body. It captures it, incarcerates it within the cell, and then depending upon what the material is, it can do everything from digest it if it's an organic material, dissolve it, or just, if it's incapable of destroying it, just keep it isolated from doing any harm by virtue of its being in this cell.

Now, these cells have a property of mobility. These cells have the ability to move. They can be deployed like a unit in any kind of a defence operation.

This mobility is governed by the need that it responds to in terms of protecting the body against the foreign invader, as it were.

Q. Now, if we go back over a number of things you said, I take it that this clearance mechanism or defence mechanism at the cellular level is the macrophages that we have been talking about for the last few days?

A. Well, it's a group of phagocytes, one type of which is a macrophage. Yes.

Q. Okay. Can you tell us why one type of phagocyte is called a macrophage, first of all?

A. Clearly, because it's a big one.

Q. Where do the macrophages come from? What is their origin?

A. It depends on which anatomic site in the body you are speaking of. There are macrophages that are formed in the marrow and circulate in the blood stream. There are macrophages that are formed in the lymphatic system of the body, the lymph nodes, and major areas of lymphocyte location or residence - the spleen, in younger people, the thymus. A third place that they are formed is within the lung itself, the epithelium of the lung, particularly down at the level we are speaking of, of the alveolar sac, the alveolar duct. The lining of these ducts and sacs are made up of different types of cells, one of which is a cell with the capability for swallowing, ingesting foreign material.

Q. So I envision that in these little sacs, or surrounding these little sacs, on the surface of them will be the macrophages that we are talking about?

A. Yes. And also some in the lining or in the hollow of the sac itself, which may come from lymphatics as well as from the lining of the alveolar sac.

Q. As you said, these kinds of cells are mobile and are able to respond to an attack or a foreign object. What causes that to occur?

A. The one word answer is a phenomenon known as taxis, T A X I S, which is the word that is used to describe attraction. It's highly involved chemistry that is associated with this phenomenon of attraction, and this attraction actually is of basically two types. For instance, you can have positive taxis where indeed the macrophage is drawn towards a foreign object, but I guess certain foreign objects having a mind of their own have the ability to repel or even dissuade a macrophage from going to this foreign object, and this is known as negative taxis.

But it's highly complex and it varies from agent to agent in terms of the medium, the milieu in which this taxis takes place. The PH or the hydrogen ion concentration of the

A. (cont'd.) material will vary for certain agents, and therefore will provide an optimum or even a hostile environment for the action of certain macrophages.

Q. Now, let's talk about asbestos and let's talk about what the macrophages do with respect to asbestos.

Can you explain that in general terms, first of all?

A. Yes. Again, being a foreign substance, the fibers will attract this defence capability and depending upon the dimension of the fiber, particularly in relation to the dimension of the cell or the group of cells, they may come out as a platoon rather than as a single scout. The fiber can...or the cells can make an effort to ingest the fiber and incorporate it within its substance, within its cytoplasm, after it's ingested, reform its cell membrane so it's again an impact cell, and for all intents and purposes this fiber is out of business, as it were.

Q. How does fiber dimension matter in terms of the efficacy of this macrophage response?

A. Because the ability to ingest any foreign material, ingest an asbestos fiber, by macrophage is determined by the size, so that a macrophage, let's say thirty micrometers in its greatest dimension, even after it contorts itself to try and ingest this thing, that is up against a fiber which has a length greater than itself, it will be just physically incapable of ingesting the entire particle. So that is a battle, so to speak, in which the macrophage has undertaken something it can't accomplish.

There are other ways of furthering the defence mechanism, but this is the critical factor - the ability of a macrophage to just mechanically engulf the fiber if it's going to neutralize it and fulfill its role of protecting the body against the effect of any foreign agent.

Q. I guess I am envisioning that short fibers will be engulfed more readily than longer fibers.

A. Yes, sir.

Q. When we say that a fiber...let's just say one ten microns in length, two microns in diameter, for purposes of discussion...when we say that that fiber is engulfed, what does that mean and what happens to the fiber?

A. Well, a totally engulfed fiber that will live within the macrophage and the macrophage itself will attempt to do things to this fiber. It will liberate within itself certain digestants, certain enzymatic materials, in an effort to destroy the foreign material. In the case of organic materials, the macrophages do this with considerable success.

In the case of inorganic materials, in the case of an asbestos fiber, it does it with rather less success, and the fiber just lives in the macrophage.

Now, the macrophages are not eternal. They have a life of...it varies, thirty, forty days...it will vary. In any event, when the macrophage dies, this ingested fiber is liberated. The death of a cell is associated with dissolution of the cell membrane, and liberation of its contents.

Now, the chemistry of the previously ingested fiber has really...or its altered chemistry...has not really been worked out all that well. But the little we do know suggests that it is an altered fiber, and it has been altered in a way that again, I think, data would suggest is less capable of inducing an adverse tissue response.

Then it subsequently, still being a fiber, is reingested by other fibers. (sic)

DR. UFFEN: Altered chemically or physically?

THE WITNESS: Altered physically. Chemically, there is a change in the ionic structure, there may be a leaching of certain cations from the fiber itself, but the real chemistry

THE WITNESS: (cont'd.) of the altered fiber has not been worked out as yet.

But it is a different fiber, and one can show this in in vitro systems, perhaps, more readily than one can in an intact animal system.

DR. UFFEN: Does it look like sort of a skeleton of the old fiber, or an actual different shape?

THE WITNESS: No, no. It's the old fiber. It is not...the shape has not been significantly altered.

MR. WARREN: Q. Let's stay again with our engulfed hypothetical fiber. It has been engulfed and thirty days later, forty days later, the macrophage dies off and we have a fiber once again in the lung. You say data suggest that that fiber has been altered in a physical sense so that its toxicity is also altered.

Can you tell me what data you are talking about?

THE WITNESS: A. These are in vitro studies that have been done, I think, by primarily in the United Kingdom...I can get you...I'm trying to think of two names of people who have done this work. During the break just let me go through some bibliography I have.

Q. Let's put the names aside for a minute. You can tell me those after the break. But tell me what kind of an experiment those two gentlemen in England did in order to reach such a conclusion?

A. What they did was in vitro experiments...that is, experiments in tissue culture rather than in animal systems...and then studies the effect of the recovered fibers after one passage, as it were, and compare them with the others. It's as straightforward as that.

Q. In other words, what they were able to do was to test first fibers before any macrophage response and to judge in a tissue culture what their toxicity was, and then compare that

Q. (cont'd.) against similar cells, similar fibers which had gone through this process of engulfment and to make a comparison of the response seen in the tissue culture?

A. Yes. They were not...these were differences that were demonstrable in the laboratory. A bioassay on the differences in the fiber, I think, has yet to be done.

Q. Couldn't be done?

A. Well, it's yet to be done.

Q. When you say that this was tested in an in vitro system, what was the inpoint?

A. Toxicity to the cell.

Q. I see. It was just cytotoxicity. All right.

But these data suggest that that fiber which had been engulfed has a reduced toxicity following the death of the macrophage?

A. I think this is the consensus of workers in the field, yes.

Q. Now, before we go on to talk about longer fiber and what happens with the macrophages, we've talked...you suggested earlier that this engulfment process is a clearance mechanism, and I guess I'm still at a loss to understand precisely why that is.

How does the macrophage involve itself in actual clearance from the body?

A. It can do that in two ways. First, by virtue of its mobility, even though there are no...there is no cilia mucous apparatus at the lower arborizations of the tree, it can, as it were, just walk up the scaffolding of the alveolar membranes to that level where the escalator begins, and then get a free ride and thereby clear the lung.

Alternatively, the macrophages have the capability of diffusing into the second of the two circulatory systems in the body, the lymphatic system. Then flow through the lymphatic

A. (cont'd.) system to one of a series of depots in this lymphatic system, that we call a lymph node, which is an accumulation, an anatomic accumulation of white blood cells, lymphatic cells, including macrophages. And there it can stay and there the fiber can just live for as long, or the particle can, or the elemental material, whatever, live for the duration of the life of the host, and produce no effect at all.

Q. Let's go back now and talk about longer fibers. We have talked about my hypothetical fiber which is ten microns in length, two microns in diameter. Let's take a longer fiber. Let's take one that's two microns in diameter but is forty or fifty microns in length.

How does the macrophage defence system respond to that longer fiber?

A. Well, it can respond in several ways. First the macrophage itself may try to go it alone, and it it's incapable of fully ingesting the fiber, so that you have like a candy apple, where the macrophage is the apple and the fiber that hasn't quite gotten in all of the apple is the part you hold it with.

Now that part there has penetrated the cell membrane. Inasmuch as the cell has been incapable of engulfing it entirely, the area where it pierced the cell membrane is not an airtight seal, and more importantly, because the cell membrane is not intact, you have essentially a devitalized cell, a weakened cell, so it cannot react the way a normal cell will.

But it will respond to that part of the particle that sticks into the cell by again liberating these digestants, these enzymes, and there is one postulant that really this is how the phenomenon of fibrosis takes place in the lung, and that is, an incompletely phagocytized, or swallowed, cell, will allow leakage from the cell of those enzymes which the cell was thinking it's liberating to dissolve what's in it, and the digestants...

A. (contd.) protease, as they are called, because they dissolve proteins, are virtually incapable of distinguishing between host protein or alien protein. It just knows that it sees a mollecular configuration that it can chew up, as it were.

Since the lining of the alveolar sacs, like all tissues, has as its base protein, this liberated enzyme indiscriminately begins to dissolve the protein which holds the normal architecture of the avleolar space and the bronchiolar space, and you have tissue death. That is one concept of how fibrosis takes place, that it is really the liberated enzymes from macrophages which have failed in their job, for whatever reason, and they have liberated these proteolytic, these protein dissolving materials.

So that's just one of several things.

MR. WARREN: Dr. Mustard has a question.

DR. MUSTARD: Can I ask a question, and the question is obviously related to my own areas of interest.

In the process of cell proliferation in vessel walls related to atherosclerosis, the most recent evidence we have is that the monocyte which becomes a macrophage, when it's stimulated in that site produces a mitogen, and that the induced macrophage in the vessel wall will produce a mitogen which of course, therefore, is a powerful stimulus to the smooth muscle cells to proliferate.

Is there any evidence about the macrophage in the pulmonary system when it's ingesting fibers that it becomes turned on to form mitogens which are released which cause fibroblasts to proliferate?

THE WITNESS: There is a paper in the current issue of a journal...I have a reprint here which I will be delighted to give you...which reports the same phenomenon in the avleolar epithelium.

May I give you the...I'll give it to you during

THE WITNESS: (cont'd.) the break...I'll be glad to give you the reprint.

But apparently, this is, according to these workers at the National Institute of Environmental Health Sciences, they are seeing a direct mitogenic effect in the alveolar epithelial cells, the analog of your smooth muscle cells.

DR. MUSTARD: Maybe we should have it introduced as evidence. I think it's...at the appropriate time.

MR. WARREN: Fine.

Do you want to take a break right now, John?

MR. LASKIN: It's up to you.

MR. WARREN: I would rather keep going, I think, because I'm logically still on this subject.

MR. WARREN: Q. Let me see if I understand the additional element that I think you've added to what we have been talking about.

As I understood Dr. Kotin's initial response to my question before Dr. Mustard's question, what I was hearing was that the fibers essentially pierce the cell and that the enzymes which are contained around that cell membrane leach out of the cell and because they are functionally designed to eat protein, they drip onto or fall onto the wall of the alveola and eat a hole in it?

THE WITNESS: A. Yes.

Q. That's basically... Now, that's awful simple-minded the way I stated it, and as I understand it, Dr. Mustard was adding an additional element having to do with mitogens, which I frankly don't understand. Maybe one or both of you can explain it to the layman.

THE WITNESS: Dr. Mustard, please.

DR. MUSTARD: It is simply a substance within cells that, when it's released in contact with the membrane of another cell, will induce the cell to divide...that is, to

DR. MUSTARD: (cont'd.) proliferate and make more cells. I guess the major development in biological sciences, both in terms of the process we are talking about here when you repair yourself when you cut your hand, is that the macrophage does have the capacity to form a mitogen when it is stimulated, and that that mitogen can be released at these sites and affect the cells in the area to divide and proliferate.

I guess in the case of the lung, the argument would be that this would produce increased proliferation of the type of cell, the fibroblasts, which would contribute to fibrosis.

MR. WARREN: Okay. I think I understand it.

What the suggestion here is, is that not only that the enzymes which are designed to eat protein, as I put it, are leached out, but also that these enzymes act as mitogens...no, not act as, produce, induce?

DR. MUSTARD: You wouldn't call the mitogen an enzyme.

MR. WARREN: Okay. Not act as. They induce mitogens which in turn generate the cell division which results in fibroblasts for connective tissue forming in that area where a hole is made by having been eaten by the enzymes.

Is that stating it with some degree of simplistic...

THE WITNESS: It's compatible with both, yes.

MR. WARREN: Q. Right. But what Dr. Mustard has added then, to this hypothesis, is not only that the enzymes are causing the damage to the structure of the aveloli, but that also the enzymes trigger the process which generates the proliferation of fibroblasts, which constitute the connective tissue known as fibrosis.

Correct?

THE WITNESS: A. Yes.

Q. You say, in response to Dr. Mustard's question, that this phenomenon has been seen in a study addressing this issue

Q. (cont'd.) with respect to asbestos?

A. It has been reported, yes.

Q. Okay. Can you elaborate a little more on...I recognize we will put the study in the record...but can you elaborate for us what that study tested and how it reached such a conclusion or observation?

A. It was a study aimed at determining what we are addressing, the issue of fibrosis and response, to exposure to asbestos, and it was exploring different possibilities, different mechanisms, for fibrosis. This is one of the observations made. It's a very early observation, it's one that is associated with just acute exposure, its relationship to ultimate fibrosis cannot be determined by this set of experiments, which will contine for years to come. It is apparently a dose-dependent observation. It takes an accumulation of fibers to do it, so I normally would not have mentioned it had not the question been asked and I thought perhaps my knowing it automatically made it mandatory that I had to let you know about it.

I think at this stage of the game it is an observation which points more to needs for additional studies rather than the basis for drawing any conclusion right off.

Q. This process that we have been talking about is, as you say, as you have said both here in oral testimony and I think you say in tab three, one of the explanations for... possible explanations for fibrosis in the lung.

First of all, can you tell us in simple layman terms what fibrosis is?

A. Fibrosis is a scar formation, I guess, reduced to its simplest form. You see, every tissue is not endowed with the same capability to restore its original cellular structure or its original framework. Some tissues have enormous capabilities

A. (cont'd.) to restore their initial structure. For instance, the liver of an animal. You could remove as much...or in a human being...you can remove as much as a half to two-thirds of the liver and the regeneration process will restore the liver so that...at least in animals where you can make the necessary studies...four months later you could never tell that this animal had any of his liver removed. That is one extreme of enormous capability of regeneration.

A neuromal cell, the actual nerve cell in the brain, is at the other extreme and it has no capability for regenerating itself. You were born with as many nerve cells as you are going to have for the rest of your life.

Now, between the infrared and ultraviolet ends of the spectrum there are varying degrees of capability. The lung falls into an area where regeneration of parent tissue, parent cellular structure, is limited, and wherever you have the inability to restore, or a very poor ability to restore, the normal parent tissue, then the very...I was going to say cheap, perhaps better... inexpensive way the body has of filling in the void, the gap, is by a scar. I guess a burn is the experience, or a gaping ulcer or a bad cut, is the best example we know where a simple...cut your finger with a knife and you will not get a scar. A sharp knife will...the capability of the skin to regenerate itself..well, two days later you may have trouble remembering whether it was your right or left thumb that you cut. But a good gouge out of the skin, beyond the ability of the skin to regenerate itself, will result in a scar, and we all have scars.

This is the replacement of the parent tissue by the very inexpensive tissue, and by that I mean inexpensive in terms of body economy. It is a tissue that grows very, very rapidly. Its nutritional requirements are transitory, because ultimately the scar burns out and it's just a piece of dead tissue.

Well, the avleolar area of the lung belongs to

A. (cont'd.) the, closer to the poorly regenerating. It can regenerate, of course, but it has a limited capability, and particularly, even...whatever regenerative capabilities it has... if a sufficiently large enough area of the lung has its cells destroyed, for whatever reason, it is then scar tissue can come and replace the functional part. In some instances you get a combination of regeneration and scar, side by side.

So fibrous tissue is a scar wherever in the body it may be.

Q. One explanation for the fibrosis which occurs in the lung as a result of asbestos exposure, or may occur as a result of asbestos exposure, is the one we have been talking about - leaching from the macrophage enzymes which carry out the functions which you and Dr. Mustard discussed.

You noted in your article that...at tab three...that there are other possible explanations for the fibrosis which is seen. Can you tell me what they are?

A. Well, first of all, some variation on the question that Dr. Mustard asked, and that is, it has been known that certain materials can have a direct stimulating effect on scar tissue without necessarily going through the antecedent or the precursor step of having tissue destroyed.

In other words, you can get fibrosis as a result of direct stimulation of these fibroblasts, which is a fancy name for the cells that make connective tissue, by direct stimulation. That is an example of another mechanism.

Q. Let's stop on that one for a second. That one, in a sense, separates out the second of the two functions which you and Dr. Mustard discussed, and it might suggest, for instance, that in the macrophage, or as a result of the macrophage having been pierced, that enzymes or something else in that macrophage induce, in turn, the creation of antigens which turn on the fibroblasts. That's one possibility?

A. Fibroblasts can be turned on, yes...and for other materials, other fibrosing experiences, as it were, a macrophage factor has been identified.

Q. That's the next question I was going to ask, and that is, we have discussed in these hearings other kinds of damage to the lung as a result of other agents. When you say that macrophage involvement has been demonstrated for other kinds of chronic respiratory impairment in the lung, what are examples?

A. I think one example which would almost encompass what we really know about is in the instance of silicosis, where indeed the role of the macrophage has been documented in a way that is infinitely more precise than has been documented for the role of the macrophage in asbestos. Here, a cytoplasmic component of the macrophage, a cytoplasmic component has been identified in which resides, perhaps, among other things as well, the capability to induce fibrosis after exposure of the cell to free crystalline silica.

That's, as it were, how silicosis...the fibrosis in silicosis gets initiated and then progresses.

Q. We've discussed two kinds of mechanisms that might explain the observation of fibrosis as a result of asbestos exposure in the lungs. Can you elucidate other possible mechanisms?

A. Highly theoretical ones. We know, for instance, that for certain allergic, in the broadest sense of the term, in some antigen-antibody reactions, particularly in the group of diseases called collagen diseases...and collagen is one of the components of connective tissue...there is a production of fibrous tissue, and the origin of those diseases or the roots of those diseases are presumably located within the immune system capability, so that it is not inconceivable that there might be an immunogenic factor. When you start talking immunogenic, you are pretty much using that big word as a euphemism for ignorance,

A. (cont'd.) really. We don't know too much about it. But it's certainly valid descriptively.

Q. Okay.

MR. WARREN: I think if we want to take a break, this is probably a good time.

DR. DUPRE: I shall assume that we want to take a break then, counsel. Shall we rise until, shall we say five to twelve?

MR. WARREN: Okay.

THE INQUIRY RECESSED

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THE INQUIRY RESUMED

DR. DUPRE: Counsel, will you proceed, please?

MR. WARREN: Q. One or two sort of followup questions on what we talked about earlier this morning.

On the use of the animal model to draw conclusions about the deposition of asbestos fibers in the lungs, what work has been done recently on this question and what does it add to the discussion which we had on that issue this morning?

THE WITNESS: A. Perhaps the most recent work would be that of Arthur Morgan at the Atomic Energy facility at Mill Hill in the United Kingdom, who has added the dimension of isotopic labelling of fibers and following them, both following inhalation as well as following their translocation within the respiratory tract, and it is clear that Arthur Morgan's work has, with more precision, by virtue of the greater elegance of his tool, pretty much confirmed earlier observations of people like Webster and his associates down in South Africa, that virtually all... certainly better than ninety-five percent of inhaled fibers in a cloud are cleared and not retained within the lung. Some figures go up to ninety-nine percent, and Arthur Morgan is continuing his studies, but as of now his published work over the last couple of

A. (cont'd.) years is verifying and getting greater precision because, as I say, of the tool that he is using - isotopically labelled fibers.

Q. I have three different articles by Arthur Morgan that maybe we ought to put into the record....simply so that material will be there so that we can refer to it in the future.

Maybe I can get Miss Jolley to make, or Miss Kahn...excuse me, two Lindas is getting me terribly confused...to make copies of these for the record.

These are the three, although they are my marked-up ones. They are my marked-up ones though. I think you have those, but we can put them in.

MR. LASKIN: Why don't you just read them into the record and we'll give them an exhibit number.

MR. WARREN: All right.

This should be exhibit thirty-one, and the three papers that I am referring to, I would like to put them in chronological order. Let me just give the names of the three.

The first one is called Fiber Dimensions - Their Significance in Deposition and Clearance of Inhaled Fibrous Dusts, and this is by Arthur Morgan.

The second one of these, which probably ought to be thirty-one B, is a piece by Arthur Morgan and two other gentlemen, Evans and Holmes, and it's entitled, Deposition and Clearance of Inhaled Fibrous Materials in the Rat. Studies Using Radioactive Tracer Techniques.

The third is an article by the same three gentlemen, Morgan, Evans and Holmes, called, The Deposition...it could be the same piece...Deposition and Clearance of Inhaled Fibrous Materials in the Rat Studies, Using Radioactive Tracer Techniques.

DR. UFFEN: Do you have a date on them?

MR. WARREN: That's what I'm...it is the same, so let's forget the last one and make it only the first two.

MR. WARREN: (cont'd.) The dates on those...the second one is 1977. It's the question of the first one, and I think the first one precedes the second one and is about 1975. But I don't seem to have the journal citations of this, so I'll have to get it.

DR. DUPRE: May I take it, counsel, that this is the same Morgan whose progress report is cited in footnote two of page 140 of tab three?

MR. WARREN: I suspect so, but let's check that.

DR. DUPRE: That is a 1976 report.

MR. LASKIN: It appears to be.

MR. WARREN: That was three...?

DR. DUPRE: Tab three, page 140, footnote two... Progress Report to the IOEH/QAMA, Montreal, 1976.

MR. WARREN: I see. I'll have to ask Dr. Kotin.

THE WITNESS: A. I beg your pardon?

MR. WARREN: Q. If you look at page 140 of tab three...

THE WITNESS: A. Yes.

Q. ...reference two, there's an Arthur Morgan Progress Report to IOEH/QAMA, Montreal, and I guess the question is, is the article we are talking about the finalization of the study which is cited by you as a progress report?

A. They cover the same areas, yes.

DR. DUPRE: It is the same Morgan, then?

THE WITNESS: It is the same Arthur Morgan, yes.

EXHIBIT # 31 A & B: The abovementioned documents were then produced and marked.

MR. WARREN: Q. Now, we have discussed these two clearance mechanisms - the mucous cilia escalator and the macrophage mechanism - and you said a moment ago that these two clearance mechanisms are ninety-five to ninety-nine percent effective. What's the basis for that statement?

A. Well, clearance studies, as I say, have been done by the group at the Pneumoconiosis Research Unit, Pooley, Timbrell and their associates at the PRU in Cardiff, Webster... Ian Webster, who is at the South African Institute for Medical Research in Johannesburg...those are at least two sets of studies that come to mind.

Perhaps I should emphasize that, this might be a good time to indicate, that all those studies, the conclusions we are talking about have meaning only to the extent that they are compatible with the dose-response and all the other elements of the study.

Q. Let me ask that. When you say ninety-five or ninety-nine percent effective, would the same conclusion hold were you talking about massive exposures?

A. Well, the same conclusion...rather than use the word massive...the same conclusion would not hold where the normal physiological capability of this defence mechanism were exceeded. In other words, all of these capabilities have a finite, all of these biological properties have finite limits which can be transgressed. Then obviously the overwhelmed defence mechanism would not be nearly as effective, and in fact would be totally ineffective. There could come a time when...we know of instances where the...you get paralysis of the mucociliary apparatus, particularly in relation to cigarette smoking where you can quantify the gradual decrease in the ability of the mucociliary apparatus to clear, or the ability of the macrophage system to ingest.

I just brought that up because as an open-ended statement it really has no meaning. You have to state it within the context of either the experiment or the clinical observations that were made.

Q. We've discussed this morning the sedimentation and deposition of fibers in the lungs, and we've discussed defence

Q. (cont'd.) mechanisms. Does it matter in this discussion whether we are talking about chrysotile or crocidolite or amphiboles, or whatever?

A. In terms of the physical biology, if there is such a thing, of the fiber, I would say the chemical makeup of the fiber would have a minimal influence. I don't know that anybody can say all or not, but I think it would be a minimal influence.

Q. Let's talk about the physical picture of the fiber, first of all, and then get the chemistry.

As I understand the chrysotile fiber, it's going to be more curly and it's going to have a different shape than the crocidolite or the amphibole. First of all, when we talk about the diameter of a curly fiber, what do we mean? I have a vision of it being different and to say diameter maybe means something different.

A. The diameter of a curly fiber is determined by the outer diameter of the helix that the curly fiber...if you envision an automobile spring, or any kind of a spring, that would be a curlicued chrysotile fiber. Well, the diameter of that fiber is determined by the diameter of the loop, and the largest loop within that helix.

Do I make myself clear?

Q. Mmm-hmm.

A. And that's what is meant by diameter, and that's how you report diameter.

Q. With that qualification in mind, and again let's keep aside chemistry for the moment, do the sedimentation rates and deposition qualities which we talked about this morning appear to apply equally to all fiber types?

A. To the extent that the fiber types would be similar dimensionally, but inasmuch as an amphibole is rigid as compared to chrysotile...or perhaps you can compare ordinary

A. (cont'd.) chrysotile with harsh chrysotile and you get away from that...it would be different if they are different. It's almost a redundancy, but if they are the same, the fact that you call one an amphibole and one chrysotile would not make a difference.

I'm stating it awkwardly, but...

Q. Okay, well...

A. ...the dimenions as a constant...

Q. ...when we are talking about deposition then, it is physics that matters and physics is the same...physics are the same, I don't know which...is the same whether applied to amphiboles or chrysotile, assuming we are talking about the same fiber diameter and length?

A. I believe so, yes.

Q. Now, is the same true with respect to the clearance mechanisms which we have discussed?

A. No. There are differences in clearance. Again, mechanisms...the more recent, as I think I referred to, elegant techniques for studying clearance are beginning to...the new data, regretably, are not constant. There are, for instance, substantive differences in the rates of clearance in the reports of Timbrell and Pooley when compared with Arthur Morgan. They are quantitative differences. They are differences, I think, that it's too early to say whether they are meaningful in terms of possibly explaining any postulated differences in biological effects. But clearly an amphibole which is a rigid fiber, which has a spicule end...you know what I mean, it doesn't have a rounded end, a soft end...opportunities for mechanical retention are postulated as being greater for an amphibole that can't mold itself to the passages and therefore gain egress, and so on.

It's still an open question in terms of the most recent data, but I guess reduced to one sentence, yes, there would be reason to believe there are differences in the clearance rates

A. (cont'd.) of amphibole and chrysotile.

Q. Based on the shape or physical nature of the fibers?

A. I believe so.

Q. It's because of this spicule end, which means it has a lot of little subfibrils coming out of the ends?

A. It's got a harsh...a Brillo pad type of end.

Q. One can postulate then that that physical characteristic makes the amphibole more likely to adhere and therefore make the...let's say mucociliary escalator less efficacious in sweeping it up into the throat?

A. Yes. In addition, there are some who feel that this sharp edge gives it an advantage in penetration through the substance of the lung. You know, it's got an auger bit, as it were, rather than a nice, smooth edge.

Q. Let's go back and just speak for a brief moment about Timbrell, Morgan, Pooley and associates, who have been looking at this kind of question in the animal models.

Is it fair to say that the hypothesis which we have been discussing of a differential retention capability has not been demonstrated by this research?

A. No, I think if you were to ask Dr. Morgan...or let's pretty much stay with the group that has been at it much longer...if you were to ask the group at the Pneumoconiosis Research Unit, they would say they are satisfied that the data support the difference in retention, with the greater retention being that of the amphibole.

Q. All right. Now, let's talk about chemistry for a minute. One of the things that come up in these hearings is a greater resistance of the amphiboles to acidic decomposition, and my question is, do you believe that feature, a chemical aspect as opposed to a physical aspect, plays any role or any significant role in the pathogenicity of the asbestos fiber?

A. I would have very great difficulty in reconciling that with the experimental observations from the self-same very fine institution, the Pneumoconiosis Research Unit.

If one looks at the experimental data of Dr. Wagner and his associates, in reasonably clean systems...by clean I mean experimentally, not aesthetically...where you don't have the confounding factors of multifactorial exposure, and so on, there really isn't any difference in the pathogenicity...if they were chemicals, I would say on an equimolecular concentration...in a fiber concentration, equivalent perhaps...between amphibole and chrysotile, he gets the spectrum of diseases, and in some instances gets more disease with exposure to chrysotile.

Clearly, the handling of the amphibole by the tissue juices, as it were, in the animal model would not be all that different. I would be surprised if it were...in fact there are no data to suggest it's different than it would be in human tissue fluids.

So that's just one reason that I question it in my own mind.

DR. DUPRE: Dr. Kotin, if I may ask, there are no data that suggest that it is different. Does that mean that there are data that suggest that it is the same?

THE WITNESS: Just the bioassay data of experimental exposure to a variety of asbestos show, within acceptable limits, an equal potential, as it were, for the production of disease. So that if indeed an ionic effect of tissue fluids on the amphibole were a critical factor in pathogenicity, I would ask the question, why do we not see it in animal models.

MR. WARREN: Q. Can you tell us a little more... the experiments which you discussed in response to the chairman, Dr. Dupre's question...what do they consist of? In other words, they are carcinogenic bioassays of what type and through what

Q. (cont'd.) route of administration?

THE WITNESS: A. Animals were exposed to clouds of a variety of asbestos types. The initial studies were done with the samples prepared for the International Union Against Cancer, the UICC samples, and these were inhalation studies done both...well, let me first stay in Cardiff, for the moment...by Dr. Wagner and his associates, in which a protocol was developed for different types of exposure, different intervals of exposure, different degrees of exposure and different materials.

Inhalation studies were also done in South Africa, and again it was a cloud study where animals were exposed in inhalation chambers under acceptable experimental criteria, and the results were as Dr. Wagner has published in the British Journal of Cancer in a series of two or three, by this time perhaps four, articles.

Q. Did the studies test in a side-by-side fashion the pathogenicity of amphiboles versus chrysotile?

A. A variety of asbestoses, including...of asbestos types...including amphibole and chrysotile. Yes, sir.

Q. In other words, the protocol specified that one group of animals received dose X of chrysotile and another group of animals received dose X of crocidolite, another of amosite, and then the inpoints from a pathological standpoint were looked at and they were within...

A. They were...

Q. ...limits which were not statistically different?

A. I didn't calculate any statistical...but basically, Dr. Wagner, I think, in his published article, noted the common pathogenicity...the commonality of the pathogenicity of the various types.

Q. Now, a question which I think has been raised previously in these hearings about the animal evidence is this, the

Q. (cont'd.) suggestion has been offered by some that to be sure the fiber types produced effectively the same result in animal inhalation studies, but that that conclusion may not be extrapolated to the human system because the retention time in the lung of humans is many years, whereas the animal model tested in the rat with a lifespan of two years, is much less. Consequently, there is in the humans a longer period of time, for any decomposition as a result of lung fluids, to take place.

How do you respond to that hypothesis?

A. I would respond by saying that telescoping in time in animal models of what happens in man is perhaps one of the few maxims in experimental carcinogenisis. Or in fact, all negative bioassay data in animal models could be challenged for the same reason. I don't buy it.

The corollary of that is not that I don't believe in dose response. I defer to nobody in my commitment to the concept, but I think that when you use an animal model, the very principle of experimental carcinogenic bioassays, by whatever method, is predicated on the assumption...we won't argue or discuss for a moment the validity of the assumption...but it's predicated on the assumption that an exaggerated dose, the artifactitiously high dose, is an adequate surrogate for the shorter lifespan of the animal when compared with man. It's an entirely different area for discussion.

So it really flies in the face of the principle of carcinogenic bioassay, because we use no species, whether it's nonhuman primates down to rodent species, that has anything approximating the lifespan of homosapiens.

Q. Okay. Can we turn to a related question on fiber types and fiber chemistry? When we were talking about the macrophage response, the macrophage engulfment, one thing we did not discuss was the so-called creation of a ferruginous body. Can you first of all explain to us what a ferruginous

Q. (cont'd.) body is?

A. Yes. A ferruginous body is a body seen...body is a bad word...it is a tissue component seen under the microscope, which has a fibrous core around which has been precipitated an iron protein colloidal complex which, because of its iron, when stained by special iron stains that the pathologist has available to him, will take on a characteristic colour which says that the stain has united with, chemically reacted with, the iron in this iron protein complex and it's there.

The fibrous core is...the presence of the fibrous core is what initiates the formation of a ferruginous body.

If you will recall, we mentioned that fibers of... speaking in terms of microscopic dimensions...fibers can be inordinately long - a hundred micrometers in length, or fifty, seventy-five micrometers in length, and what happens is that a macrophage which is clearly incapable of ingesting this material may be part of a group of macrophages which surround this fiber... again, that's almost a defence...and I guess the analogy that I can think of most clearly would be that of a sliver under your skin where you don't see it, a group of cells arrange themselves around the sliver and so a group of these macrophages, because they are incapable of ingesting the fiber or sequestering it by themselves.

Now, to effectively engulf this fiber or neutralize it, the macrophages, again through a system which molecular biology has yet not elucidated, form what we call a giant cell, and pathologically a giant cell is a cell that is not only large in size, but has many, many nuclei. The normal cell has a single nucleus and a single cytoplasmic component around which there is a cell membrane.

Now, these giant cells can be formed in one of two ways, or giant cells in general can be formed in one of two ways: They can be formed very simply by having a cell divide

A. (cont'd.) its nucleus. Its genetic material can divide. But the cell membrane itself will remain intact, house the two nuclei, be or not be...but in most cases be much larger than the parent cell was...increase cytoplasmic function, and that's how you have what we call one form of a multinucleate giant cell.

Another way for these giant cells to form, and probably this is what happens in the formation of a ferruginous body, is these eight or nine or twenty, whatever it is, giant cells align themselves around this...I'm stating it dramatically, I've never seen it happen, although I've seen electron micrographs of macrophages apposing fibrous material...these cells have the ability to dissolve their contiguous areas of cell membrane so that they dissolve the membrane and rather than having ten little balloons, as it were, each with an intact cell membrane, you have a single cell membrane encompassing all of them, and of course the residual nuclei are now part of one very, very large cell.

If you can see that the cells that make up this membrane were...and thinking three dimensionally...on all sides of this fiber, then the fiber would, for all intents and purposes, be entirely engulfed by this giant cell.

Q. A couple of questions about coating. First of all, where does the iron come from? It's called ferruginous because of the iron, and where does the iron come from to make up the coating?

A. Well, injury is almost...speaking in a pathological sense...is almost universally associated with injury to the vessel wall, but I'm speaking of vessel in the microscopic sense, the tiny capillary, the arterial or the veinal, and this injury to the vessel wall results in the liberation, the extravasation of blood into the area, blood containing iron, particularly in the red blood cells. These red blood cells, again,

A. (cont'd.) have a finite life and particularly in the alien environment of not being in the blood vessel, they are at greater risk to dissolution and the liberation of iron.

So that iron, in addition to being an essential trace element, is liberated into areas of injury from the blood vascular system, and that is a rather immediate and generous source of iron.

Q. So that the macrophages, whether it's one macrophage which engulfs a small fiber or multiple macrophages which operate together to form a giant cell, call upon available iron in order to create the coating which we are speaking of?

A. I don't think it's that purposeful. It's a series of chemical reactions which are generated by mechanisms that are still...

Q. Not at all understood?

A. ...that certainly I don't understand.

Q. Okay. So the ferruginous body, though, when we talk about something being a ferruginous body, we are not talking about a fiber that is engulfed in a macrophage or a series of macrophages. We are talking about a fiber that has a coating on it, with no cells surrounding it?

A. It can...it depends where in the evolution of the fiber you happen to hit it. You can see the residue of former cellular material.

Q. In other words, we may have a ferruginous body which has been recently coated, but the cell is still alive, and we may have a ferruginous body which was coated long ago and...

A. I believe that. I can't say that I have ever seen the chronology.

Q. One of the observations that other people seem to have made and that has been discussed in these hearings, is that the ferruginous bodies are disproportionately...that ferruginous bodies disproportionately have an amphibole core as

Q. (cont'd.) compared to crocidolite, even when crocidolite exposure is indicated. True?

A. I think you meant chrysotile.

Q. I'm sorry. Chrysotile. If you substitute the word chrysotile for crocidolite in my question, is that observation correct?

A. Yes. This is an observation that Andrew Churg has made in his studies in California, and continuing his studies at the University of British Columbia. And this is an observation that has been made at Cardiff, at the Pneumoconiosis Research Unit, and it appears that those working in the field have found a predominance of amphibole core. Yes, sir.

Q. Why is that? And I am not asking you why in the sense do you know the answer definitively, but why might one expect that to be the case?

A. Well, first of all I think, and this is...give me about thirty seconds and that will save ten minutes of talking if I can formulate my thoughts...well, I would suggest first that the ability of chrysotile, or the proclivity of chrysotile to split into fibrils rather than retain its fibrous structure...the fibrils are still fibers, of course, they still have the three-to-one aspect ratio and are just thinner...may be a factor. If we are looking for mutually exclusive differences between amphiboles, and particularly in persistence, and chrysotile, the amphibole remains reasonably intact in terms of its physical properties, physical characteristics after it has been inhaled, unlike the chrysotile which has the ability to split into fibrils.

Perhaps another reason would be the differences in clearance rates, as we were discussing before.

That speculation probably isn't worth much more than the energy involved in my giving it, but I would be really derelict if I didn't emphasize...and I'll have to think about this,

A. (cont'd.) this is almost paradoxical, if indeed the concept that amphibole has a greater pathogenicity than chrysotile, why should it be the one that shows the greatest response to a protective activity on the part of the host, inasmuch as...I don't think anybody questions the nonpathogenicity, the relatively less pathogenicity, the infinitely less pathogenicity, of an asbestos fiber that has been coated and is now an asbestos body, or core of an asbestos body...it seems a little paradoxical.

But, I would like to think about this. This is a question, I must say, I've never thought about. I'm aware of the observations, as I say, of the group at California, now British Columbia, and Cardiff. I don't know.

There's nothing about the biology that I'm aware of, which doesn't mean awfully much, I suspect, that would explain it.

Q. Let's talk about a related question. I guess it's a related question. It would appear from the discussion which we've had so far that the efficacy of macrophage engulfment is greater for short fibers than for longer fibers, simply because of the physical dimensions of the macrophage.

A. Yes.

Q. True?

A. Yes, sir.

Q. I think you have said in your writings that in your judgement the pathogenicity of long fibers is far greater in short fibers than it is in long fibers, which are the bad actors?

A. Assuming the diameter is within the appropriate...

Q. Assuming the diameter.

A. Yes, sir.

Q. True. What's the basis for your belief that the long fibers are the bad actors, as opposed to the short fibers? Is it, first of all, the efficacy, the greater efficacy,

Q. (cont'd.) of the macrophage response mechanism to short fibers than to long fibers?

A. That would be one component of the rationale.

Really, the rationale falls into two areas: One, what there are in the way of data, and then how compatible the observations are with what we know about the general area of carcinogenisis, and more specifically, solid state carcinogenisis.

Q. Let's take the first...

A. Let me address the first, if I may.

Clearly, the work of Wagner, of Merle Stanton and his associates, of Pott and his associate Friedrichs in Germany, William Smith at Barry Dickinson University, and John Davies at Edinburgh, have a consistency in terms of data relative to length and diameter as determinants of potency, with the long, thin dogma, as it were - the longer the particles, and at the same time the thinner that it is, in these experimental models, intracavitary installation in virtually all instances, there is a cutoff point for potency as distinguished from...I mean relative strength as to lesser strength, and I think...it's awfully difficult to quote Dr. Stanton, but I think Merle...and most scientists who have talked to him would agree...that he tended to lend very little credence to the sporadic tumor that he saw in animals that had not short fibers, but shorter than his eight micron fibers in length, and his one micron or one and a half micron in diameter.

So, there's this body of animal data using different models and different techniques...or the application of the same technique by different scientists...that give consistent results.

Q. Let me explore those studies for a minute, because I want to make sure that I understand and we all understand what those studies consisted of, what kind of studies were they and what were the protocols.

Can you explain, for instance, what Dr. Wagner's

Q. (cont'd.) studies consisted of, how did he test this question of fiber dimension and pathogenicity?

A. Basically what all of them did...and I think what one can say about one applies to the other, but their techniques differed a bit...they resorted to intracavitary installation, into the thoracic cavity and into the abdominal cavity, of fibrous materials of reasonably well-defined dimension, and that's the most one can say for it...reasonably well-defined dimensions in every case, I think, but Merle Stanton's, where indeed his samples were prepared with a finiteness that made each sample virtually...at least in the case of asbestos and other fibers...a research project in its own right, in other words, the standard deviation, the L-shaped curve was a very, very narrow one.

Anyway, what they did was instil this material into the cavity, making sure that it remained in place...in the case of Merle Stanton, he used a pledget initially of a fibrous glass, as the vehicle for this, and then in subsequent experiments he no longer did that...and then followed the response of the tissue in the abdominal cavity, in which case would be the mesothelial surface of the cavity and the mesothelial covering of the intestines, and in the chest, the mesothelial lining of the pleural cavity and the mesothelial covering of the lung... and looked for the production of...what the response would be.

Initially, fibrosis occurred, which was followed by the production of malignant neoplasms in certain instances, and the rodent counterpart of mesothelioma, let's say, and they were able to correlate this with the dimensions of the fiber, with the long, thin fiber being the more potent tumor producer, fibrosis producer, and the shorter fibers less potent to the point where Dr. Stanton and Dr. Wagner felt they had a dimensional configuration which had no adverse effect at all.

Q. What was the dimensional configuration which showed no observed adverse effect?

A. Again, in the literature you pays your price and you takes your pick. Some will say thicker than a micrometer in diameter, some will say thicker than two micrometers in diameter, some say three. Well, let's halve the distance and say that anything greater than two to three micrometers in diameter, and then in the length area, eight micrometers I think was Dr. Stanton's, was Merle's figure, but let's arbitrarily say five micrometers. So that a fiber shorter than five micrometers in length and thicker than two and a half micrometers proved to be nonpathogenic.

Nothing is non in a biological system, of course.

Q. Right. When you say...and I think that's worth continuing to emphasize...when we talk about numbers like eight or five as length, and two or three as diameter, we are not meaning like turning off the light or turning on the light. There is a distribution of effect, but with the effect being so small as to not be observable at some cutoff level?

A. We have very few Newtonian equivalents in biology.

Q. Now, when we are talking about the work of Stanton and Wagner and the other people that you have referred to, if we accept the observations seen consistently by those investigators, that is that the pathogenicity of fibers diminishes to not observable below five in length, two or three in diameter, from a biological standpoint how would we explain that observation, why does it make sense?

Certainly one thing that we have discussed so far is the macrophage response. Is that the explanation?

A. No, I think the explanation will lead me to the second of the two areas that I mentioned first. The concept that physical...first of all, I think it's necessary to state

A. (cont'd.) that the mechanism for the induction of cancer by a fiber, or by a solid state material - a hunk of teflon, a piece of cellophane, Bakelite, a dime, if you will, Canadian or U.S.A., it makes no difference - that the concept of the induction of cancer by those, and the mechanism, really has singularly little to do or has very little in the way of parallels with chemical carcinogenesis, and this is terribly, terribly important to emphasize.

It's startling, but the concept of chemical carcinogenesis clearly envisions some kind of an interaction between the chemical and the genetic materials, whether you alkylate one of the bases or the nucleatites that make up the DNA helix, or whether you destroy some of the genetic material so that if it survives in its damaged state it codes for cancer, really we have no such data to support this in the area of physical carcinogenesis. For in fact, whether it's an asbestos fiber or a manmade fiber, or it's some elemental material like a disc made out of elemental silver or tin or gold, or a base metal, that is implanted and produces cancer, two observations have rather consistently been made: First of all, the material never gets into the cell. This you can demonstrate quantitatively. The dime is still the same shape, the hunk of teflon is still the same shape and the same size, it even has the same molecular configuration.

So it not only doesn't get into the cell, but the cancer that arises doesn't arise from a cell that is immediately apposed to this dime, or this hunk of Bakelite, or this asbestos fiber. It is a cell layer once or twice removed from the cell layer immediately surrounding this solid state material.

Now, this was an observation made by Prayne and his associates, oh, many years ago at the National Cancer... originally at the University of Washington in Seattle, and then at the National Cancer Institute.

A. (cont'd.) I think it's an observation that Bischoff at Santa Barbara, who has worked for many years in solid state carcinogen sis, has verified, and more recently and infinitely more elegantly, again only because the passage of time has allowed for more elegant techniques, Professor Brand at the University of Minnesota in Minneapolis has shown that solid state carcinogenesis...there is a mystique, and again that's a euphemism for ignorance...but the concept of interaction between the genetic material that occurs with a chemical, an alkylating agent or a frameshift mutant, or whatever you have, does not take place there.

But what is very interesting is that you can modify the carcinogenicity of an agent in solid state carcinogenesis by modifying its physical charactertistics. This can be done precisely.

So that a hunk of teflon, the teflon, the dime, a nickel, it doesn't make any difference, that will produce a cancer by installation under the skin of a rat, or in the brain of a newborn mouse as Zimmerman has done with teflon discs and so on, film, if you take this and alter the physical characteristics of this...and how can you alter the physical characteristics of a dime or a hunk of teflon...punch holes in it, do nothing more, reimplant the fenestrated, as it were, the windowed plastic material, and maintain everything else at constant, you have obliterated the carcinogenicity of that disc or that film.

DR. UFFEN: Can I ask, does it depend on the nature of the solid? There comes to mind something that you might regard as a solid - gypsum, another mineral. And you stick, instead of a dime you stick some gypsum in, and it doesn't cause cancer. Is it somewhere in between the chemical ones and the solid ones?

THE WITNESS: Calcium sulphate has been...it's good

THE WITNESS: (cont'd.) to use that as an example... that has been studied, and the explanation for that is residence time. Calcium sulphate is particularly susceptible to neutralization, to dissolution and removal by tissue fluids.

DR. UFFEN: So it's not a true solid?

THE WITNESS: Exactly. You don't have residence time.

DR. UFFEN: You stick something like titanium or magnesium...

THE WITNESS: You've got cancers.

DR. UFFEN: Or sodium?

THE WITNESS: Again, as I look and try to recall the literature, I can't recall that anybody has ever used sodium, because that would present certain other methodologic problems. If you use sodium as salt and even made a hardcast pellet out of the salt, it still would be subject to...

DR. UFFEN: How about as a silicate?

THE WITNESS: That is interesting in the sense that one of the questions asked by students of pneumoconiosis is why the fibrosis-cancer sequence in asbestosis and not the silicosis-cancer sequence in fibrosis.

There are suggested postulates, not the least of which is that indeed there is an increased risk of cancer in persons exposed to silicosis, and only modern techniques of data analysis are beginning to show this. It's highly speculative. Nobody is really claiming it, but certainly it is ore that is being mined by the biostatisticians and epidemiologists.

But there is a difference in the sense of the silicosis because the nature of the fibrosis in silicosis, and this is just one man's opinion, is an exuberant short period between the fibrosis and its being burned out, when it becomes an essentially nonviable scar. And further, the location of the fibrosis in silicosis - the interstitial nature of the fibrosis in asbestosis creates a special problem for the

THE WITNESS: (cont'd.) epithelium, because one of the interesting phenomena in asbestosis is that when you do get a cancer of the lung in a person who has been exposed to an adequate dose of asbestos, and I think we can talk about that, that lung cancer is an increased risk in the nonsmoking asbestos worker - let's accept that for the moment, it is interesting that the cancer of the lung is an epithelial tumor, a tumor of cells that line the tracheobronchial tree, not a tumor of the connective tissue where indeed the initial stimulus for cell growth has taken place. One can ask the question, if asbestos is that potent a carcinogen, why does it not stimulate cancer in the fibrous connective tissue cells which are present because of the sequence of events that we have already described?

Well, this is relative to the silicosis question because you don't see the same type of an epithelial response in silicosis. It occurs in a different place and the fibrosis itself is a different type.

I hope it's clear. If it isn't, it's my fault rather than the fact that...

DR. UFFEN: I can't claim that it's entirely clear, but you answered my question better than anybody has yet.

THE WITNESS: Thank you.

Well, to come back, so here you see the concept of fiber being the determinant, of a dimension being the determinant for a carcinogenic property of a solid state material does not only, to use a double negative, fly in the face...it does not fly in the face of accepted principles of carcinogenisis, but actually is entirely compatible with them.

If you were to take...and let me use the example of another solid state material, some tin or gold or silver...and had it in a series of different dimensions from rock candy size to granular sugar size to powder sugar size to triple X powdered sugar size, and kept everything constant in terms of the amount

THE WITNESS: (cont'd.) you put into the animal, where you put it into the animal - the same species, as you got to smaller and smaller dimensions, you would obliterate carcinogenicity.

So that a gram or an ounce or a ton of granular gold or granular lead will produce cancers under the skin or in the brain, whereas the same ounce or pound or ton in super powder sugar equivalent will produce no tumors.

MR. WARREN: Q. Okay. Now, this afternoon after lunch we are going to come back to many things which were imbedded in Dr. Uffen's question, and so I don't want to make it appear that we have left them behind. We'll get that after lunch.

But if I can summmarize the...what you are saying about the biological plausibility of the findings of Stanton, Wagner, et al, it is that the shorter fibers in length and thinner in diameter do not...right.

Well, let's turn it around the other way, that the longer fibers and the thicker fibers are more pathogenic than the opposite. That's true perhaps because of the greater efficacy of the macrophage defence system, but in addition to or maybe related to that point, is the point that the long series of data and observations over a number of years on solid state carcinogenesis support the plausibility of there being a size below which little pathogenicity should be seen.

THE WITNESS: A. Yes.

Q. Is that a fair summary of what you...

A. It is a fair summary and I think you adequately emphasized the plausibility and the like, because hard data are not there.

MR. WARREN: Okay.

I think this is a good time for a lunch break, in my book anyway.

DR. DUPRE: Shall we rise until 2:15 then?

THE INQUIRY RECESSED

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THE INQUIRY RESUMED

DR. DUPRE: Counsel, just before we begin, I assume that what we have here are the two Morgan articles, that they are exhibit thirty-one, namely A and B?

MR. WARREN: Yes.

MR. LASKIN: Correct.

DR. DUPRE: This morning, just before we had our break, in answer to a question by Dr. Mustard, Dr. Kotin, you referred to a reprint you had just read. Is this the same as exhibit thirty-one?

MR. WARREN: Linda says exhibit thirty-two, right?

MS. KAHN: If you are entering it.

MR. WARREN: Why don't we enter it then?

DR. DUPRE: ...which we do not yet have?

MR. LASKIN: We will provide it.

DR. DUPRE: All right. Thank you.

MR. WARREN: Q. Dr. Kotin, this morning we had a lengthy discussion of deposition of particles in the lung, of clearance mechanisms. What I would like to do now is to talk a little bit about cigarette smoking, and the first issue I would like for you to address is how cigarette smoking affects the clearance mechanisms which we discussed. Could you explain to us how cigarette smoking affects the mucociliary clearance mechanism which you discussed this morning?

THE WITNESS: A. Yes. Cigarette smoke, of course, is a highly complex aerosol with some literally thousands of compounds...many of them highly toxic. Cigarette smoke affects the

A. (cont'd.) mucociliary apparatus in two ways - first it affects the mucous biochemistry, the ratio of the various constituents of cigarette smoke, various constituents of the mucous, is altered in epithelia which has been exposed...in an epithelium which has been exposed to cigarette smoke.

The initial response is to first result in a thinning of the mucous...the chemistry is irrelevant for the moment...followed by a thickening of the mucous, increase in viscosity, and simultaneously the cigarette smoke has a specific inhibitory effect on the ciliated cells.

What it does is interfere with the transmission of energy from the cytoplasm of the cell to the cilium itself, so that initially and very, very transiently a ciliated epithelium exposed to cigarette smoke undergoes an increase in rate which lasts really...measurable in seconds, as though purposefully it's trying to get rid of it, and this is followed by a slowing of cilia in an orderly way so that you still have the beat, a constant one like a crew rowing, but they are doing it at a much slower rate. Ultimately, there is disorganization of the beat, leading to attentuation of the motive power, and ultimately you get total paralysis of the cilia, and with this and since it's the motive power for the mucous blanket, the result is a stagnation of the mucous. So that what happens is that particles that are deposed, deposited, I should say, on the epithelium just remain there. They are not carried away towards the throat for removal, and I think the analogy to an escalator is a valid one.

It's as though in a department store an escalator were to stop, but people were still to continue coming on and on and on, and so you ultimately would have rather than one layer, piles and piles of people trying to occupy the limited space.

The result of this, of course, is that it provides one of the necessities that we referred to this morning of

A. (cont'd.) increased residence time for whatever biological effect you are going to study for.

So in essence, what it does is neutralizes more effectively than perhaps any known toxic agent that I am aware of the effectiveness of the mucociliary apparatus.

Q. Okay. Let me try to go back over some of the things that you have said and try to put some sort of a time dimension on them, or a dose dimension, or both.

The first thing that I think you said was that with respect to the mucous layer itself, that the cigarette smoke, the aerosol chemicals contained in that cigarette smoke, have a chemical effect on the mucous - first thinning it and then thickening it.

Now, could you tell me first when you say first thinning and then thickening what time dimensions you mean by 'first' and 'then'?

A. The time dimensions are very, very rapid. They are measurable in minutes, but the recovery in an initially exposed epithelium is equally rapid, so that a puff of cigarette smoke will result...smoking one cigarette would be a better way to put it...will result in a rapid, highly-transient effect on the ciliary apparatus in terms of motive power and any change on the mucous probably would not come through until you perhaps smoked the equivalent of a pack of cigarettes within a one day period. You would begin to see changes in the...

Q. So that the initial...the second of the two effects that you are talking about is the one that is most acute in its time dimension, I guess is what I'm trying to suggest. When you smoke that cigarette and looking again at, you know, the time frame of a half an hour or an hour or something like that, that cigarette has an initial impact on the motive power or the efficacy of the sweeping mechanism of the cilia?

A. Measurable and a very, very brief period of time, as you say.

Q. Now longer term...and again, I would like to know what longer term means in response to this question...in the longer term, the cigarette smoke itself can have a chemical effect on the composition of the mucous itself?

A. Yes, sir.

Q. Why is that, first of all, and when we say over a longer term, what do we mean?

A. Well, the effect of cigarette smoke on a mucous-secreting cell is the effect of, as I say, a highly complex aerosol containing groups of compounds - acroleins, cyanides, organic acids, aldehydes, alkaloids - a whole array of alkaloids - and the nicotines and/or nicotine dienebasine, which are all highly cytotoxic materials. Fortunately, they are all rapidly metabollized materials at the low dose of a single cigarette, and so on.

So the time frame would be related to the intensity of smoking. It would be dose-dependent. I really can't give you a time other than to say the measurable response under laboratory conditions in both laboratory animals and in dynamic studies on volunteer human beings shows a very, very rapid induction of the effect.

Q. So to begin with, and again without defining dose, it's kind of hard, I recognize, to define time, but in an acute sense the mucociliary clearance mechanism is almost immediately affected by cigarette smoke?

A. Yes. Transiently.

Q. Right. Now, you say transiently because if I smoke one cigarette or maybe even a pack of cigarettes a day, and don't smoke for the rest of my life, those effects which we see in an acute sense dissipate over time and at some point in the future no impact would be discernible?

A. I don't think you have to stop smoking the rest of your life. I think laying off for a period of a couple of days..

A. (cont'd.) because you must remember that the regenerative powers of the respiratory epithelium are very, very great because it represents one of the interfaces between the living organism and the external environment, so that a great reserve has just, on an evolutionary basis, been built-in to this epithelium.

Q. Let's talk about the effects of chronic smoking, and now I'm talking about the man who is smoking a pack a day over years.

A. Okay.

Here you have a clearly demonstrable series of chronologic effects. Habitual smoking, let's put it this way, or chronic smoking, or whatever, will result over a period of time in an increase in the activity of these mucous-secreting cells...and again, if one is to look at it purposefully, as it were, I think any secreting surface will try to dilute the toxin, among other things...so that you find an increase in the ratio of mucous cells to ciliated cells.

If you recall that picture on page three in that...

Q. Let's take a look at it though, because I think it's useful.

A. All right. If you will notice, there is a ciliated cell, a nonciliated cell, a mucous-secreting cell.

Well, after a period of time, the mucous cells begin to increase in number and size, compressing the ciliated cells, as it were. Finally, this increase in size results in a pressure death not only of the cells that secrete the mucous themselves, but the ciliated cells themselves. These cells that die are desquamated. They are peeled off, leaving the basal layer of cells, the cells which sit on the membrane, that delimits the lining of the lung or the trachea or the bronchi, and they undergo regeneration, they multiply to replace this denuded

A. (cont'd.) epithelium, as indeed it happens on the skin, in the cervix of the uterus, or in the mouth, any epithelium surface.

Well, what happens is, because of the fact that cigarette smoke not only contains irritants, toxic substances in the acute and subacute sense, but also contains carcinogens, you create a situation where you get optimum opportunity for the carcinogen to interact with the cell at the basal layer, the generative layer of cells, the cells that multiply to replace the cells that have peeled off.

Now, it is only a cell that has retained its capability to divide that can produce a cancer, and that applies throughout the entire animal species...animal kingdom...so that the mucous cell, the ciliated cell, in and of itself cannot produce cancer. From a generative point of view, it's for all intents and purposes, dead. It's alive from a functional point of view, but...

Well, anyway, these cells in the basement layer the basement membrane cells, the generative layer of cells, undergo replication and reproduce ciliated cells and mucous-secreting cells, but you are continuing to smoke and by now it's the third year or the fifth year that you have smoke, or the eighth year that you have smoked. The irritant effect begins to be added onto by the carcinogenic effect of the tobacco smoke.

Now, the cancer-producing chemicals in tobacco smoke begin to affect that basal layer of cells, so that after a critical period, measurable in years, these cells begin to multiply in a way that doesn't reproduce the ciliated or the mucous-secreting cell, but reproduces a more primitive cell - primitive speaking from the point of view of embryonic development, phylogenetically or autogenetically, and this primitive cell results from two reasons, as much as we understand: One, the stimulus

A. (cont'd.) to regenerate on the part of those basal cells is a very, very rapid one in the sense of its constantly being exposed to a carcinogen, and it begins to get some of the hallmarks of a carcinogen action. It begins to multiply much more rapidly.

Secondly, the carcinogen itself begins to interact with whatever it interacts with in the cells...for the moment let's say the genetic material. So you begin to see the first waystation on the long road to the development of a cancer. You begin to see what we call hyperplasia and metaplasia, both of which mean excessive growth and altered growth.

Q. Let me go back over a number of things before we get too far down the road on this.

Just mainly for purposes of clarification, for our chronic smoker that we are talking about here, the smoke causes an irritation which induces the generation of more mucous, as you say, to dilute the effect of the toxin. That's the first kind of thing that happens, right?

A. Right.

Q. The body permits that additional mucous to be created by a proliferation of the mucous cells, right?

A. Correct.

Q. Now, if we look at the diagram, this figure one, as you said, what we have are alternating mucous and ciliary cells.

A. That isn't exactly the way it is. I just put it there for...

Q. Right. But I mean schematically that's a fair representation of it?

A. Right.

Q. I mean, they don't alternate as...but schematically this is a fair representation, I take it?

A. Yes.

Q. When, the ciliated cells are those cells with

Q. (cont'd.) the little hairs sticking out, and the mucous cells are those which don't have such hairs sticking out, right?

A. Correct.

Q. Now, what happens as a response to this chronic insult from the cigarette smoke is, we begin to see two, three, four, mucous cells alongside each other, and then a ciliated cell, and then three or four more mucous cells, and so forth. Is that sort of what happens?

A. That's what is happening.

Q. Eventually we find what, that we kill those ciliated cells?

A. Yes. Basically they have a finite half-life to begin with, a finite period, but basically the pressure that they are undergoing, the abnormal physiology that they are undergoing, the abnormal function that they are undergoing, is not compatible with their survival for any prolonged...

May I go to the board?

Q. Sure.

A. This is the airway, and here are the cells, some ciliated and some mucous-secreting, and sometimes we call them goblet cells because the globule of mucous of here with the stem leading down to the base gives the appearance of a goblet.

Now, underlying these adult cells is a layer of cells is a layer of cells which we call the basal layer of cells. It is these cells that give rise to these adult functional cells. These cells have the potential for producing different kinds of cells. They are primitive in the sense of having retained this multipotential.

But what happens is, as the person continues to smoke you begin to find that these goblet cells, these mucous-secreting cells, begin to secrete more and more mucous...much of it going out into the lumen...but more of it being retained.

A. (cont'd.) And there is a corollary of that here... and let's make this a ciliated cell like this...you get a mucous puddle or a pool of mucous here. This is compressed.

Ultimately what is going to happen is that this is, the vitalized layer of adult cells is going to peel off. What's going to happen is these basal cells will then be called into action to form, divide and form, a new layer of cells not unlike that which peeled off.

Q. Let me ask...interrupt for a minute to ask...why do the cells eventually peel off?

A. They die. They undergo necrosis. They undergo death as a result of their devitalization, their abnormalities, in fact, but they have been poisoned.

Q. I see.

A. Now, if we repeat this quite literally a thousand times, what is going to happen is the epithelium, the basal generative cells, is going to begin to have to multiply a little more rapidly than it would like to and again, oversimplifying it but not really taking any liberty with biological facts, you find that it begins to produce a combination of two types of regeneration: One, the layers of epithelium as we saw it, the ciliated cells and the mucous cells. But also it's going to reproduce an embryologically more primitive type of cell, so that here you have side-by-each, as it were, as one looks in the microscope, an area of reasonably respectable and identifiable-looking respiratory epithelium, and here you have an area of hyperplasia, which means excessive growth, and metaplasia, altered. There are two things to remember about metaplasia - regeneration with metaplasia, the term metaplasia means that the new cell that is formed to replace this functional cell is, from an embryological point of view, a more primitive type of cell. It has one with a greater potential for doing many, many things.

The second thing is, that up to a point this

A. (cont'd.) metaplasia is reversible.

If this person, after the fourth year, stops smoking and indeed months pass, he may peel all of this off and reconstitute his epithelium so that in looking at it you would never know that he smoked.

The second thing I just mentioned in one sentence, if you recall this morning the discussions about the lungs and branchings, this metaplasia is...again with biological exceptions... first seen at these areas of impingement as the aerosol or the fiber or what-have-you, comes down the trachobronchial tree.

Okay, now, this metaplasia, as I say, can do one of three things. It can revert to a normal state if the stimulus is removed, it can remain static, or it can progress.

The way it would regress is to move in the direction of cancer by beginning to develop some of the characteristics of cancer cells in these cells, and the characteristics to a pathologist would be that he would notice that instead of having a constant and acceptable ratio of size between cytoplasm and the nucleus, the nucleus would begin to get a little larger. So the nucleus-cytoplasmic ratio is disturbed, indication that the genetic material in one way or another is being acted upon.

Q. Let me try to interrupt again so that we don't get too far away from...I mean, all of this I want to cover, every bit of it.

When we begin to see cell death of the ciliated cells, and then a peeling off of the mucous and ciliated cells, certainly at that point the process is entirely reversible if the stimulus, the cigarette smoke, is withdrawn. Correct?

A. Correct. Yes, sir.

Q. That's true even if it happens a thousand times? Or, you know...

A. Nobody has ever counted it, but...

Q. But the point is that it can happen many times and still the process is reversible if the stimulus is withdrawn?

A. Remarkably so, yes.

Q. Now, at the same time, during this process of repeated generation of new cells, the continued presence of the toxin causes the cells which are generated out of the basal layer to be different than originally?

A. Yes.

Q. That's what we are talking about when we are talking about metaplasia or hyperplasia - hyperplasia is just a proliferation of those cells, and metaplasia is a changed cell in some sense or the other?

A. To a more primitive cell.

Q. Okay. Now, what is it again that scientists believe happens to cause the process to extend beyond hyperplasia and metaplasia to an actual neoplasia, which you have described pathologically as a difference in the character of the cells in terms of their shape and their regularity, and so forth?

A. There are volumes describing it, but all they are is description. Nobody knows.

Q. I take it that...well, let me ask the question, is the...we talked this morning about solid state carcinogenesis. Now, is the assumption for cigarette smoking that we have a similar mechanism operating?

A. The assumption with cigarette smoking is that you have...this is a poor representation of the genetic material...you have compounds here which determine what we are. What we are is determined by a buzzword called a code, that determines or distinguishes a mosquito from an elephant.

Now, what the action of a carcinogen is assumed to be, is to interfere by chemically uniting with one of these chemicals that make up the genetic material...

Q. The DNA.

A. The DNA. ...and doing it in such a way that the DNA no longer codes for at least one thing...it just proves we can see, it doesn't prove that we know anything...and that is the growth-controlling protein within the cell.

Every cell must have a growth-controlling locus so that when we cut our hands, when the wound is repaired, or a peptic ulcer is healed, a message comes to turn off making more cells because the defect has been repaired.

So whatever this growth-controlling protein might be, it is apparently knocked out of the lexicon of that DNA in a cancer cell, so that stated very, very, very simplistically, the DNA is coding for a cancer protein as distinguished from a normal protein.

Q. Okay. Now, I take it that for cigarette smoking that's because some chemical component of the cigarette smoke actually interacts with the DNA and produces this kind of miscoding or mistake?

A. Not one, but an array of chemical agents that provide the necessary ingredients in the two recognized steps in the formation of a cancer: One, the changing of the cell, and then the series of subsequent changes which takes that altered cell and has it grow into becoming a clinical cancer.

Q. Okay. Now, you were talking a moment ago about where we begin to see...again, we are putting aside asbestos, we are talking about cigarette smoking and cigarette smoking alone for the purposes of this question...where do we begin to see the, physically, in the body, the cancers resulting from cigarette smoke?

A. In the lungs, you mean?

Q. Right, in the lungs.

A. Well, you mean at what level?

Q. First of all, let's step back a bit and say where do we begin to see the kind of cellular alterations that

Q. (cont'd.) you are talking about? Where in this schematic diagram of the body?

A. In the...you can see in the lung, the entire surface from the first branching of the trachea down to the bronchioles, down to the tubes that lead into the air exchange area, the alveolar duct and the alveolar spaces.

Q. Okay. Now, I take it that that's where, if this process continues long enough, that's where you begin to see the lung cancers as well?

A. Right. You can see lung cancers as a result of smoking, they can be seen anywhere along the tracheobronchial tree. We have what, in jargon, I guess, the people who work in the pathology of lungs call a central tumor mass. That can happen anywhere along the tracheobronchial tree.

Q. Yesterday when Dr. Becklake was here, she made a distinction and I've seen others in the literature make a distinction between two different cell types of lung cancer, and they were, I believe, squamous cell carcinoma and adenocarcinoma.

A. Yes.

Q. Can you explain the difference between those two?

A. Yes. Well, the skin...first of all, they are descriptive in the sense of what the pathologist sees, looking through the microscope. A squamous cell is the cell that normally lines the oral cavity, it is the cell that covers the skin, it is the cell that covers the uterine cervix...that's three of many, many places that have squamous cells...and what it is, is without labelling it, so I was drawing what a pathologist sees under the microscope as squamous cells, a basal layer of cells and then layers of cells on top. This can be the skin, the cervix, the mouth. It could be the esophagus, it could be any one of many, many sites.

Now, a cancer that has the appearance of having originated from cells of this type is called a squamous cell cancer.

A. (cont'd.) You can see, if we jump to where we are going to go, how a squamous cell cancer of the lung can occur, but only after there has been metaplasia of the normal mucous ciliated epithelium to squamous epithelium. I know perhaps no more potent inducer of metaplasia than cigarette smoking that can lead to cancer.

There are other things that induce metaplasia, but that's irrelevant.

In contrast, adenocarcinoma represents a cancer from a glandular portion of the epithelium, so that if this cancer were to arise from only basal cells again, rather than go through the metaplasia, these basal cells suddenly decided to produce abnormal mucous-secreting cells, you then would have a cancer, still derived from the same basal cells, but there the configuration under the microscope would be more nearly like the normal counterpart, the usual counterpart of the epithelium, the glandular portion.

Of course, that glandular epithelium becomes a secreting one.

So those are the two types of cancers that Dr. Becklake referred to.

Q. Okay. Now, let's go back to asbestos and what happens in the case of asbestos. One of the things that we know from the discussion we have had is that even immediately the clearance mechanism is affected by cigarette smoking because of the impairment of the function of the cilia. I take it as this process continues, the impairment becomes greater?

A. Yes.

Q. To say the impairment becomes greater is just another way of saying that the effective dose of asbestos which reaches the lungs and stays in the lungs is increased?

A. That's right.

Q. You said this morning that the clearance mechanism

Q. (cont'd.) might be ninety-five to ninety-nine percent effective for fibers, and I think we said that depended, of course, on dose. If there was a heavy dose, it might be less effective.

Would you say the same thing in the case of a cigarette smoker? In other words, would the cigarette smoker be able to have ninety-nine percent effectiveness of the clearance mechanism?

A. He would have his clearance mechanism interfered with. He would have an abnormally higher retention of particulate material, fiber in this case, asbestos fiber, would certainly be retained to a greater degree than it would be in the nonsmoker.

Q. Okay. So that clearance...so we know that in the case of breathing in asbestos, if you are a cigarette smoker you have an impaired ability to clear the lungs and therefore have a greater effective dose in the lung, of asbestos?

A. Yes, sir.

Q. What other effects may cigarette smoking have in connection with asbestos exposure, which could lead to the synergistic effect which various studies have reported?

A. Well, it would further interfere with the other area of defence that we spoke about before, and that is macrophage action.

Q. How is that?

A. Well, cigarette smoke, no more or no less than asbestos, is a foreign material, so the same macrophages are mobilized to ingest the chemical components of cigarette smoking. In fact, the histologic picture is rather characteristic. A person will look in a microscope and say, ah, these macrophages are full of pigment. It takes a certain stain which clearly has cigarette smoke as its source.

So that basically it is a competitor, as it were, if you will, for macrophage activity. Cigarette smoke is a,

A. (cont'd.) since the supply of macrophages is very, very great, but not inexhaustible, it will ultimately deplete...not completely, but reduce the number of available macrophages, and then the macrophage distended and laden with cigarette smoke pigment is one that is not available for other things, just as the macrophage which has ingested an asbestos fiber has done its task, and so on.

So that is the second worry that cigarette smoke...

Q. So....cigarette smoking strips away both of the defence mechanisms which we talked about this morning...

A. It attacks them both.

Q. ...both mucociliary escalator and the macrophage defence system?

A. It affects both, yes.

Q. Okay. Now, how about...is there any significance to, or is there anything important about how the macrophages deal with cigarette smoke as compared to asbestos fibers? For instance, we talked this morning about the proteins in these liposomes. What do we know about that process with respect to cigarette smoking?

A. Basically, since the ingestion of the products of cigarette smoke do not compromise the cell membrane of a macrophage, you don't have the analog of the leaking of enzymes, protein digestic enzymes, and in fact this is wholly compatible with the fact that the toxic effect of cigarette smoking on the lung, other than cancer, is not one of fibrosis. It is one of obstruction - bronchitis and emphysema, because you don't have the equivalent...many a time you will see what you interpret as a macrophage which has burst under the extreme dose of cigarette pigment envelopment in the macrophage, but even that doesn't initiate the process of fibrosis.

Q. If we now ask ourselves a question, what we discussed with cigarette smoking, how we see a process going

Q. (cont'd.) from toxic effect to hyperplasia and metaplasia, and assuming a direct impact on the DNA, a neoplasia, can we attempt to discuss whether there is any kind of a similar process with respect to asbestos, and in particular whether there is any relationship, or what relationship is there between the creation of the...the causation of fibrosis and the ultimate tumor which appears in the lung?

A. There are several components to your question. First, cigarette smoking, in addition to its physiologic effects, enhancing retention and so on, provides an altered epithelium and an altered epithelium is at increased risk to whatever comes along, and particularly in this instance, to cigarette smoke itself in relation to cancer induction, and to the added effect, the synergism is the word I believe you used, that has been demonstrated epidemiologically in cigarette smokers who simultaneously are exposed to asbestos.

Epidemiologic studies have shown this enhanced risk for persons exposed to both.

Now, as far as the fibrosis in relation to the generation of cancer, as I mentioned earlier, one, the cancers that are, I believe, associated with and caused by the combined exposure to cigarette smoking and asbestos exposure are the result of the fibrosis interfering with the normal physiology of the epithelium so that it is susceptible in a much more sensitive way to the action of any adverse agent, including a carcinogen.

The phenomenon I am speaking of is a phenomenon known as scar cancer, and it's something that has been known for many, many years, if not, in fact, decades.

The first observations of scar cancer were made when a group of people, Paul Steiner at the University of Chicago perhaps as much as anybody, identified a series of cancers adjacent to scars, but they were not cancers that arose from the scar tissue, they were cancers that arose from the epithelium.

A. (cont'd.) They were carcinomas.

But, he postulated, and since then I think data has pretty much verified this, that the scarring of the connective tissue has, immediately adjacent to the epithelium, has been so altered that any carcinogen that came along could, at a lower level of exposure, perhaps initiate a sequence for cancer.

So that scars have a definite role, I believe, in the genesis of the increased risk to lung cancer observed in asbestos workers.

Q. Okay. It's all getting very, very complicated for sure, but if we look at asbestos alone, and let's withdraw cigarette smoking for a minute, we postulated this morning, based on the evidence which you discussed, a mechanism...or maybe a couple of mechanisms...that might cause the fibrosis, and those mechanisms effectively, as you and Dr. Mustard discussed, would result in the creation of fibroblasts or fibrous tissue, connective tissue, in the lung structure.

Now, I guess what you are saying is that the presence of that fibrous tissue causes subtle effects which weaken adjacent epithelium and which may therefore make it susceptible to insult from other toxins or other carcinogens. Is that it?

A. Yes, sir. Exactly.

Q. Would it be fair to say from that statement of fact or evidence that asbestos doesn't itself cause the cancer but instead produces a weakened state which allows some other carcinogen to initiate a change in the epithelial tissue, which in turn results in a neoplasm?

A. Not in every case.

Q. Okay. Now, explain why not.

A. First of all I think we have to acknowledge that asbestos, both on the basis of clinical studies and experimental models, is capable of inducing a neoplasm on its own.

A. (cont'd.) It is a carcinogen.

Now, in the lung peculiarly you have a situation where the dose that would induce a neoplasm of the lung is one that, in the absence of cigarette smoking, has done this exceedingly rarely. It has done it in a way that...at least from my point of view...always have to have, if you are going to suggest that asbestos is responsible for a bronchogenic carcinoma, has to have the scarring, the asbestosis, beforehand, which provides the suitable setting for the action of the carcinogen.

So in some, you would have to say that the rare cancer of the lung in a nonsmoking asbestos worker could indeed be related to the asbestos, but at least to satisfy, I think acceptable criteria of diagnosis, you would have to have...or of pathogenisis, you would have to require the presence of asbestosis as the antecedent.

Q. From this discussion, the way I understand it, you are saying that while cigarette smoking is not in all cases a necessary antecedent of lung cancer for asbestos workers, the presence of some fibrosis, given the biological models we are talking about here, is a necessary antecedent?

A. Yes.

Q. Okay. Now, when you say that this situation that I have just spoken of, that is a carcinoma in the lung in the absence of cigarette smoking is rare, does that suggest that in the vast majority of situations the likely initiating event in producing the carcinomas is the cigarette smoke?

A. I'll perhaps state it more positively. I will say in virtually all, allowing myself the biological escape hatch that nothing is always or never.

Were it not for cigarette smoking, I think whatever other asbestos-related diseases or health problems there might be, lung cancer would not be one of them.

Q. In any...we have already discussed that one

Q. (cont'd.) cannot rule out lung cancer as a result of asbestos exposure, for the reasons we have discussed and the mechanisms that we have discussed.

A. Yes.

Q. But in comparing the two parts of the problem, you come away then with the conclusion that cigarette smoking is the vastly predominant factor?

A. Vastly.

Q. All right.

Now, let's talk a moment about mesothelioma, which we haven't discussed at all.

First of all, can you tell us how these fibers we discussed this morning entering the nose and going through the trachea and so forth do get to the pleural or the peritoneal tissues?

A. I'm sure there's more than just one way. The fibers can enter the...well, let me just back up by saying that the membranes that separate the various pockets of the alveolar sac have this epithelium we spoke about, but in the core of the membrane there are blood vessels, there are lymph channels, and fibers can get into these highways, as it were, and travel, and they can travel to the surface of the lung or the pleura.

Another way that has been postulated is the fact since inspiration is a forceful muscle-controlled activity that the mere act of inspiration can mechanically, at very, very slow rates of speed, move fibers towards the outer surface of the lung towards the periphery.

Another way that has been suggested is that by and large the fibers themselves find a potential space, and the body is made up of various potential spaces that can be infiltrated.

The mere fact that you have to have three explanations and preface them all with 'may' is a pretty good

A. (cont'd.) indication that we really don't know. I don't think there is any real data to suggest what the predominant mechanism is for the translocation of fibers to the pleura. It's probably all three.

Q. So we don't really know how they get there, except we know they get there?

A. I think so.

Q. And we know they can cause sarcomas in the mesothelial tissue?

A. Correct.

Q. Now, I am right, am I not, that the kind of tissue we are talking about in the pleural or peritoneal is a connective tissue much like that connective tissue that we spoke of when we were talking about fibrosis?

A. Well, it's a mesothelial tissue that is derived from the same germ layer. It's really not a connective tissue in that sense.

Q. Okay. The thing that I would like for you to explain to me is, I think you noted earlier that we don't see the tumors in the lung in that fibrous connective tissue. Instead, we see it in adjacent or next-to-adjacent epithelial tissue. Yet in the pleural cavity or the peritoneal, we see those tumors in a different kind of tissue altogether. How do you...or maybe altogether is too strong a word, but in a different kind of tissue.

From the standpoint of mechanisms of cancer production that we have discussed this afternoon, how would one go about explaining that?

A. First of all, I think physiologically mesothelial tissues and mesothelial cells have a number of functions. One is obviously to line or cover visceral organs.

Secondly, mesothelial tissues have the capability of, not with the force that macrophages have, have the ability to

A. (cont'd.) ingest foreign materials as well. Basically, mesothelial tissues are indigenous and physiologically at home, as it were, where they are, in contrast to fibrous tissue, no matter how rapidly it is proliferating, if it's being.... if it's proliferating in its capacity of providing cheap replacement for functional tissue, it's in an unphysiologic site responding to a pathologic rather than a physiologic stimulus.

So that there is a difference between the two.

Q. Okay. What's the explanation? I mean, what do we know, what do we know and what can we say about what happens? What kind of process is there which produces these tumors in that tissue?

A. First of all, we have the umbrella of ignorance of not knowing really for any malignant neoplasm at the DNA level or at the molecular level what the lesions are, what are the events that are responsible for the causing and then the perpetuation of cancer.

But one can say certain things. One is that there seems to be, and certainly in the experimental models where you can quantify the situation, there seems to be a correlation between...in some experiments, this isn't even consistent...between proliferation of the mesothelial cells and ultimate development of a mesothelioma.

In other experiments, this correlation does not exist.

I hope I got it right, but we can always go to the record, Stanton did not routinely see a correlation...or I guess Stanton did see a correlation between proliferation and mesothelioma formation, and I think Bill Smith did not.

Again, I think these are experimental observations that represent the same experience of two observers with workers, responsible workers.

A. (cont'd.) But there is no question that the induction of mesotheliomas, if you follow it exquisitely in experimental models, shows the equivalent of change that I described in the lung - the hyperplasia, the metaplasia, the metaplasia with atypism because the metaplasia is not nearly as easily discernible there, but you get an altered cell, then you get an atypical cell in the sense of the alteration of the DNA as seen not biochemically but as seen through the eyes of the pathologist and so on, which leads on to a malignant neoplasm.

And that's all one can say. One can only describe what one sees. One really cannot, on the basis of existing knowledge provide a mechanism.

Q. It would be fair to say then that we know an awful lot less about what causes, or the chain of progression... cause is maybe too strong a word anyway...the chain of progression to neoplasm in the pleurae or peritoneum than we do in the lung?

A. Oh, much, much less. Yes.

Q. Now, I take it that, nevertheless, for all the reasons you have discussed this morning, you would expect this to be a dose-related phenomenon?

A. It would almost have to be an unexplainable exception if it were not. It not only is...I don't see any way that it couldn't be a dose-related phenomenon.

Q. I have only got one short additional last question and then I'll turn to other things.

One of the implications that emerges from a practical standpoint from the discussion we had this afternoon appears to be that cigarette smoking is a more important factor to be concerned about, in the broad scheme of things, than asbestos in the working environment. Would you agree with that?

A. Yes, and the data clearly support that.

Q. I know that J-M has had a program of attempting to reduce cigarette smoking among its workers, and I wonder if you

Q. (cont'd.) could give us a capsule summary of how that program works and what success you think it has achieved.

A. Well, the program essentially was initiated by having a protocol for discussing the rationale for a ban on cigarette smoking with all the workers, and this was done on every shift, in every plant. We are satisfied, without college degrees and so on, our workers know as much about the basic physiology of the lung as many a sophomore student, I felt.

Anyway, then what we did was establish...there are two sides to the policy: One was the policy that if persons could be exposed to asbestos, a condition of employment was being a nonsmoker.

For smokers, a nonsmoking, a kick-the-habit program, was instituted which consisted of making available...and it was varied from plant to plant because of the difference in the availability of programs for kicking the habit...it was a program that was for the worker and his or her spouse, recognizing that if one stopped, the husand or the wife stopped and the other didn't, you were reducing the likelihood of success.

The company had agreed to pay for the fee for the programs, where there was a fee, for both the husband and wife, or the spouse, and two of the large no-smoking programs refused to accept work...as much as they wanted a new contract...refused to accept a contract on the basis that there ought to be some commitment on the part of the worker to the program as measured tangibly in dollars. So what we did was pay half the fee, with the stipulation that the remaining half would be returned to the worker if, after a year, they were still not smoking.

And if after the original smoking, kick-the-habit program, it didn't work, they could go back again and go back a third time.

The understanding was for them to get rid of the smoking habit. That was the primary...all right.

A. (cont'd.) Now, the program is now in its third or fourth year of implementation...second year. We have had our share of problems, many of them self-generated, but I would say...and one cannot generalize because the cultural influences in different parts of the country in relation to smoking differ considerably, so Oregon is not Louisanna is not North Carolina is not New Jersey...so in some plants we have had very, very little success...little success, three to four percent having kicked the habit and stayed off the habit. In some plants, as much as thirty-five, forty, forty-five percent kicked the habit and have stayed off the habit.

So we are continuing the program and it was a program that has been challenged both by our...many of the unions...not many, several of the unions in some of our plants have challenged it, and I must say at no time was a union challenge ever predicated on the validity of the data. Their challenges were on the basis of violation of collective bargaining...you know, things that fall into the industrial relations area, and not the health safety area.

Even where we would appear before an arbitrator and the union would say we are challenging this rule, it was made very, very clear that we are not challenging the validity of the data, we are just saying the company has no right to do this the way they did. Obviously that was something that was between the industrial relations and the spokesmen for the locals at the various plants.

The grievances have gone to arbitrations three or four times. In Texas, the arbitrator held that we could not ban smoking, but would have to provide smoking areas and we were within our rights to limit smoking to these areas at prescribed times.

We appealed this to the Surrogate Court, and the

A. (cont'd.) Surrogate Court upheld the union's position.

In other areas, in Florida, Massachusetts, the arbitrator held that the company had the authority to do this when the grievance was filed.

So we are continuing the program, repeating the educational dimension of the program, the visual aids with other materials that tend to reinforce the need for and the wisdom of the program, and that's where we are right now.

Q. I take it that this smoking program has been coupled, over this whole period of time, with attempting to keep your asbestos exposures low through normal controls?

A. Yes. Well, basically the challenge that this was a way to circumvent compliance with regulations was made, and since industrial hygiene measurements are a matter of universal knowledge, just by the requirements of the Occupational Safety and Health Act...at least for the last decade...the workers have known what constitutes our industrial hygiene findings in the plant.

Q. Okay.

MR. WARREN: I think that's about it for me.

DR. MUSTARD: Can I ask some questions related to your discussion this afternoon?

MR. WARREN: Surely.

DR. MUSTARD: Because I haven't had your usual elegant summarizing of the whole story.

MR. WARREN: I've failed again.

DR. MUSTARD: My questions come a bit out of some of the summarizing and some of the things that maybe we could amplify a little bit.

MR. WARREN: Okay.

DR. MUSTARD: First of all, it's the pleural scarring that occurs with asbestos exposure. Would you regard the

DR. MUSTARD: (cont'd.) mechanism there as biologically essentially similar to what we are talking about in the lung? Is that a similar kind of mechanism?

THE WITNESS: I am hesitating for one reason, and that is: One does not necessarily see the necrosis antecedent to proliferation in many mesothelial areas of cellular proliferation. In other words, you don't have the necrotic area being replaced by fibrous tissue in some of the mesothelial areas.

DR. MUSTARD: But the macrophage is identified there, is it not, at some stage?

THE WITNESS: Oh, yes. And basically, the mesothelial itself is sort of a pseudomacrophage at times, when it assumes that role.

DR. MUSTARD: The reason for the question is that you commented, I believe, in the dialogue this afternoon, that scarring in the lung was, in your view, a prerequisite for carcinoma of the lung.

THE WITNESS: Mmm-hmm.

DR. MUSTARD: I was wondering if we could take the same analogy for mesothelioma, a scarring of the pleura is also a prerequisite, and if it's not, if you have any explanation?

THE WITNESS: I have none, but...

DR. MUSTARD: But do you get that...if you dig hard enough in the pleura will it show scarring is present in the pleura if mesothelioma occurs, or does mesothelioma occur without there being evidence of fibrosis?

THE WITNESS: You can see mesothelioma without evidence of scarring. In fact, you can see phenomenal scarring in populations which have no increased risk to mesothelioma, as I'm sure has been said. Anthophyllite is a potent producer of pleural change, and one doesn't really see mesothelioma in anthophyllite-exposed populations, and further, I think it's fair

THE WITNESS: (cont'd.) to say that despite extensive studies, a relationship between pleural thickening and increased risk to mesothelioma has not been identified.

In areas where pleural changes are very, very common, one doesn't see the difference in risk to mesothelioma that one would anticipate if pleural thickening were antecedent.

DR. MUSTARD: All right. Now, going back to just before lunch when we had solid state tumors, sort of to close that off, we hadn't perhaps completed the full dialogue that could go on there, because I think you implied, if I'm correct, that the asbestos fiber was behaving like a dime.

THE WITNESS: Yes, sir.

DR. MUSTARD: Is that a correct interpretation?

THE WITNESS: Yes, sir.

DR. MUSTARD: The asbestos fiber then caused something to occur in its interactions with the macrophage in the tissues which led to the cells lining the lung to develop a neoplastic characteristic. In other words, that there was some kind of transmission of signal, and we never did talk about what your thoughts might be about the transmission of that signal that might affect the lining of the lung, and it would help me a little bit if you could amplify that.

THE WITNESS: I can answer...

DR. MUSTARD:: Am I right in my...?

THE WITNESS: You are absolutely correct.

I would answer that by saying that it is my belief that since virtually all cancers of the lung in asbestos workers are in smoking asbestos workers, that the role of the asbestos per se in the genesis of brochogenic cancer is an indirect one...that you do not get, it is not the asbestos fiber that produces the cancer of the lung...it is the asbestos fiber that provides, in the case of cigarette smoking, a substrate effect for the increased effectiveness of cigarette smoking in

THE WITNESS: (cont'd.) inducing cancer.

And in the nonsmoker, it provides no less than the old TB did, or a focus for the action of any carcinogen or any... both exogenous or endogenous, that can induce the neoplasm.

I don't believe that asbestos per se is a pulmonary carcinogen, except in very, very, very rare instances.

DR. MUSTARD: Then how would you explain the mesothelioma, then? Can you take the same argument that the mesothelioma is not directly caused by the asbestos fiber?

THE WITNESS: No, because basically in the mesothelioma you would have the space, the solid state material, the asbestos, in the tissue, giving rise to the neoplasm.

DR. MUSTARD: Still...

DR. UFFEN: Without macrophages?

DR. MUSTARD: No, no. The macrophage is present in the pleurae, and what I'm really trying to get at is, to put it bluntly, is if you are going to have some kind of mechanism by which the solid fiber can cause the cells lining the pleurae to become neoplastic, if that involves the macrophage why can the same process not operate in terms of the lining of the alveolae and the bronchioles?

THE WITNESS: Well, the macrophage is a mediator. It provides a substrate for the activities. The macrophage itself has nothing to do with carcinogenesis other than preparing the soil, as it were. The macrophage brings to the site, in the case of the lung, the wherewithall to produce the scarring. It brings with it the tissue necrotic component.

May I go to the board for a minute? Maybe that might help.

DR. MUSTARD: You might want to, while you are at it, dispose of what I recall as an old theory, that when those enzymes leak out or release that they may be endosarcous, taken up by other cells, and may have some damaging effects...

THE WITNESS: Yes, I think that is still a viable position.

DR. MUSTARD: You might like to explain that, because that could be a direct causal effect, could it not?

THE WITNESS: It could be. Yes, sir.

What Dr. Mustard is referring to is the fact that not only do the liberated enzymes...and I'm going to get my candy apple drawing here...if this is a macrophage with an asbestos fiber ingested in the nucleus of the cell, well, this is not an airtight seal and this is where enzymes are leaking.

Now, the question you were asking is if these enzymes are in the cell, why are they not chewing up the cell itself. Well, the reason they are not is they live in a separate little bag, and the bag is called the lysosome bag.

What happens is that this penetrating fiber, in the course of penetrating, destroys some of these bags and liberates these enzymes. These enzymes can chew up alveolar walls, but then in addition to that, by a process which can really be seen under the electron microscope only, called pinocytosis, these enzymes are capable of being ingested by other cells and, since they are highly-active materials, they can be capable of stimulating the proliferation of the cell which has...let's put this in the form of an X. Now, this X can do two things, as I say. One, it can dissolve the lining of the air sacs. But in addition to that, this X can be absorbed into some of the cells right along here, without destroying them, and causing them to proliferate and lay down connective tissue.

It is this latter phenomena that you are referring to, is it not?

DR. MUSTARD: Well, I was even going further. There was a theory proposed, without much evidence I suspect, that that may even modify the basic cellular components here,

DR. MUSTARD: (cont'd.) leading the abnormal proliferation of the cells...in other words, a neoplastic proliferation.

DR. UFFEN: Can it get into the nucleus? Can the enzymes get into the nucleus?

THE WITNESS: No. If they did...proteolytic enzymes that got into the nucleus would almost certainly kill the cells, because what they would have to do is...you see, the DNA just, except in viruses, does not sit naked. The DNA is coated... COATED...it has an envelope around it of proteins, which we call nuclear proteins, and these are proteins which are primarily histones and the like, which protect the DNA and also modulate the DNA.

These nuclear proteins would be susceptible to digestion by these proteolytic enzymes that come out of here, and I would seriously doubt that a cell could survive that had these things. So...

DR. MUSTARD: But through the mechanisms of leukocytes and the other part of the component, RNA, the thing called reverse transcriptase, you still would have the probability of modification in the non-nuclear area, the cytoplasm, and that means head back to the cell's normal machinery, to the DNA. But that's probably not this probe. I just tried to probe the question as to whether, because of a problem of the mesothelioma and the lung cancer, whether you couldn't have a basic similar mechanism in both areas that are setting cells up to become neoplastic.

THE WITNESS: But the reverse transcriptase, you have your RNA virus there, and you don't have the equivalent there. You've got a self-limiting material.

If you had a self-replicating protease, then I think that theory would have a greater likelihood of being correct.

THE WITNESS: (cont'd.) Now, the mesothelioma in... okay, this represents the mesothelial surface of the chest cavity. The presence of the asbestos fiber here provides it with, I believe, the appropriate milieu, the appropriate setting, for solid state carcinogenisis principles to apply, and this has been observed, I think, most noteably by Professor Brand, who in the current issue of Cancer Research has a paper on altered chromosomal patterns within the cells immediately surrounding...and I think in this case he might have used glass, he might have used asbestos, I don't know...but in any event, in the mesothelium you have this presence of a fiber. In the respiratory epithelium, the only place where fibers have been identified has been in the alveolar duct and distal to the alveolar duct - the site of perhaps less than one percent of all bronchogenic carcinomas.

Even the alveologenic carcinomas, the cancers that you see in the alveolar area, are as a rule preceded, as I'm sure you have seen many times, by bronchialization of the alveolus. You see the bronchialization of the alveolus, and it is those bronchializes alveoli that give rise to even these terminal cancers....a bona fide type one cell cancer is about as rare as they occur. They occur only very, very rarely.

So that I reserve solid state carcinogenesis for the pleura and really don't feel it is particularly relevant to the lung because I don't believe alone asbestos is a pulmonary carcinogen.

Now, this asks the question then, is there such a thing as an organ-specific carcinogen. Well, an organ-specific carcinogen chemically and an organ-specific carcinogen in the physical sense are two entirely different terms.

Chemically, there probably isn't. Organ-specific physically, there is.

I don't know if it answers your question.

DR. MUSTARD: Thank you.

MR. WARREN: Q. Let me see, since I failed to summarize before, if I may do so now, just so that I do understand it.

You have asked the question why, if we are talking about solid state carcinogenesis in the pleural cavity, and if we are comparing what is happening in the lungs with asbestos, first of all why we are not seeing fibrosis or why it isn't, as in the lung, a necessary precursor of the tumor in the pleural cavity, and secondly, whether the mechanism might not be the same.

This is a question to Dr. Kotin: If that is a fair statement of the question, what I am understanding your answer to be is that the mechanism which is occurring in the lung is not really solid state carcinogenisis for asbestos. Instead, what is occurring is that the fibrosis generated by the process we have been talking about causes a substrate effect which in turn weakens the defences of the adjacent epithelial tissue to the initiating effects of other carcinogens, including cigarette smoke, and that it is in that sense, and that sense only, that asbestos is implicated in lung cancer.

By contrast, in the pleural cavity, the mechanism is much more closely akin to, if not identical to, the production of tumors through a solid state mechanism like the dime you were talking about this morning.

Is that a fair summarization?

THE WITNESS: Yes, sir.

Q. Now, okay...

DR. MUSTARD: I have one final question to ask. When you dose animals with asbestos fibers, you can get lung cancer, I believe. Isn't that correct?

THE WITNESS: Yes, sir.

DR. MUSTARD: The animals are not smoking.

Do the animals all show scarring, fibrosis of the

DR. MUSTARD: (cont'd.) lung, in relation to those tumors, or do some of them get tumors without scarring?

THE WITNESS: I think they show scarring.

DR. MUSTARD: Do you have a reference for that?

THE WITNESS: I think...well, the man who has done... perhaps produced as many tumors, is Dr. Wagner, and I understand he is going to be here...I hope it's Wagner.

Yes, Chris Wagner's three papers in the British Journal of Cancer...I'm sure you have them on file...where he shows in the photomicrographs productive fibrosis.

MR. WARREN: Okay.

DR. DUPRE: Shall we break until four-fifteen, and you will perhaps get together with your colleagues to put your arms around the geography of...

THE INQUIRY RECESSED

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THE INQUIRY RESUMED

DR. DUPRE: Counsel, do you wish to begin?

MR. LASKIN: Thank you, Mr. Chairman.

All set, Dr. Kotin?

CROSS-EXAMINATION BY MR. LASKIN

Q. Dr. Kotin, I think what I would like to do is take the valuable lesson that you have given us today in biology 101, not all of which I purported to understand, and see if I can marry it to some of the things that we have already learned in epidemiology 101, and see whether the union that we get is a happy one or not.

I guess what I would really like to do is explore issue by issue and find out whether the biologic evidence is consistent or not consistent with the epidemiologic evidence.

Q. (cont'd.) I take it if we find some consistency, then we can be relatively confident that we are on the right track, and if we find inconsistency, then we've got to start looking for some explanations as to why one doesn't match the other.

Is that fair?

A. That's fair. Absolutely.

Q. Let me start with the question of fibers and different fiber types, if I might, which is of some interest to the Commission.

Let me start with that issue in relation to mesothelioma, and the evidence that we have heard so far, at least as I apprehend it, from most sources, is perhaps best summarized by what the Simpson Report in Great Britain said, and I wonder if I might just take the liberty of reading to you their essential conclusion on that point and let me see whether you agree with it or what your reaction is.

I read just a sentence from paragraph eighty-one at page fifty-three of the report, which says:

> "As far as mesothelioma is concerned, evidence from miners, from process workers exposed to a single fiber type, from the distribution of neighborhood and domestic cases, and from the geography of mesothelioma when combined presents a powerful case from four different sources that crocidolite has been more dangerous than chrysotile and anthophyllite, and the position of amosite may be intermediate".

Insofar as you understand the human epidemiologic evidence, is that a fair assessment of what we know?

A. As written by an epidemiologist, yes. As written by somebody who would be taking a global approach, I think there are some unanswered questions.

I think if indeed workers are exposed to a higher

A. (cont'd.) concentration, in this case of crocidolite, than to any other type of asbestos, they are at greater risk to disease.

As I think was observed earlier in the day, dealing with an amphibole, which by its very nature is more dusty, by its very nature is more likely to result in a higher level of airborne respirable particles, exposure would be to a greater dose.

So I think that is the critical thing that has to be evaluated.

I will not quarrel with the epidemiological data where they have seen, as indeed the Simpsons Report contains in its bibliography, the bodies of data from four sources.

I would ask three or four questions: Number one - first I would ask is the exposure of the crocidolite population, with its enhanced risk, the equivalent of the exposure fiber-by-fiber, if you will? I don't think there is a satisfactory answer now, but I think there is one in the offing with the advent of body burden studies, the studies that perhaps began with...not began with, certainly have been done to a degree by the group at the Pneumoconiosis Research Unit, by Britwell in the U.K., by Vigneau in France. These are all preliminary data.

Now, if indeed it can be shown that on a fiber-for-fiber basis exposure results in increased risk to mesothelioma from crocidolite, clearly that will be a fact.

I would submit that all the information is not in.

Q. Is it fair to say, and I take the point, is it fair to say that in the way in which we seem to have found these fibers so far, in the workplace, whatever happens to them, whether it's because of the shape that they are in when we naturally see them in the workplace, that the epidemiological evidence would seem to suggest that crocidolite in fact is more hazardous?

A. Yes. My speculation was that the epidemiologic

A. (cont'd.) evidence says that. Now, whether the epidemiologic evidence represents a true...is a true reflection of the biological potency of the material fiber-per-fiber is something that I would submit as yet we really don't know. Because we do have certain time-honored questions that are always raised. One has to do with if one amphibole, why not others. If it's crocidolite, why not anthophyllite?

This can almost be reduced to...if somebody were an avocate for one or the other...to a red herring type of question.

The issue of Transvaal versus Northwest Cape, many suggestions have been offered, explanations given. Again, I'm not satisfied, but whether I'm satisfied or not is irrelevant.

I don't think the data are such that from a biological point of view, fiber-per-fiber, the case has been made.

Now, what would it take to make the case convincing? I think the populations are there, the gas-mask workers is a special population. There are other single-fiber exposure populations, and in a matter of time I think the question is going to be a self-resolving one when body burdens are done and are correlated to attack rates.

Q. Well, to take two single-fiber populations which have come before us, namely Dr. McDonald's large cohort study in Quebec, which I know you are familiar with, and Dr. Dement's more recent study of South Carolina textile plant, as I understood both of those studies, they were chrysotile fiber exposures only, insofar as we know, and in both cases the incidence of mesothelioma was, relatively speaking, quite rare. Indeed, in respect of Dr. Dement's study, although there appeared to be a fairly significant excess risk of lung cancer, there was nonetheless only one mesothelioma.

Have I fairly stated it so far?

A. You have, and I think the McDonald and the Dement data, at least that facet of the Dement data, cannot be

A. (cont'd.) glibly dismissed. I, just for myself, feel that the totality of information at present lacks one or two aspects, and it can be reduced to one sentence, and that is - the dose of exposure.

But if it can be shown dose for dose that amphibole and crocidolite, with amosite as the intermediate, is more potent than chrysotile, I have no vested interest in either and I'm perfectly happy to acknowledge that. But I think to say, by the same token, I would like those added bits of information.

Q. When you say dose for dose, do you also mean dose for dose within the same industrial establishment, or would you be prepared to say dose for dose with textiles on the one hand and mining on the other?

A. The differences in attack rate between textiles and mining are so great that they are axiomatic. Right now we are reduced to saying there is just something different between the two. We really don't know what the difference is, other than the epidemiological data, other than level of exposures. So I think, if I understand your question, I acknowledge differences in...in fact make a strong point of the fact...that differences in circumstances of exposure can clearly be reflected in differences in attack rates, and this applies for virtually all carcinogenic agents.

Q. As I understand some of the epidemiologic studies, just pursuing this one point about fiber differences, there were at least two studies - one by Dr. Enterline and the other by Dr. Weill - where they were able to give us some observations at least on differential effects as between fiber types within the same cohort. Is that fair?

A. Both Dr. Weill and Dr. Enterline think they have, and I have discussed it frequently with Dr. Weill and Dr. Enterline, and I'm not so sure of the discrimination between the exposures being as discreet as I would like them to be...as I think they should be to convince me.

A. (cont'd.) Really, I have no qualms in this. They are now concerned with the position that crocidolite is an inducer of mesothelioma, as it is an inducer of other asbestos-related problems. I just really am more plaqued by the few paradoxes or internal apparent contradictions, and they may not be real ones, than I am by the consistencies - particularly when the likelihood of exposure to a higher dose is so compatible with what we know about amphibole and its dustiness.

Q. What are the paradoxes?

A. The Northwest Cape/Transvaal, anthophyllite/crocidolite. Those are two substantive ones.

Q. Is there anything in the biologic evidence, including the shape of the fiber and all of the things that you talked about this morning, which would lend support to any differential effects between the amphiboles on the one hand and chrysotile on the other?

A. If those were the only...if that were the only area of information available to us, clearly one would have to suspect the amphiboles more than chrysotile.

Q. If what were the only area of information?

A. Just the difference in the type of fiber, its handling in the lung and so on. The thing that we mentioned this morning of the rigidity of the fiber, the likelihood of its being retained, the likelihood of its penetration. The amphibole there, I think one would have to responsibly state, is more likely to produce a local dose effect.

Q. When you give that evidence and you put the caveat, 'if that were the only evidence', what else are you thinking about?

A. I guess what I'm thinking about is something that is so, I believe, readily at hand, and that is just doing some body burden studies and relating them to disease.

I guess if...my position...I would feel more

A. (cont'd.) untenable if I were asking for some innovative new trail-blazing research. All I think I'm asking is that some existing techniques...admittedly difficult, but no more difficult than many of the things that are being done everyday in the field of asbestos research...be applied to a problem, with some real dispatch. I think it can be done with real dispatch.

I guess I find myself in the uncomfortable position of having to sound like a defender of crocidolite, which heaven knows is about the farthest things from my mind, but basically I think there are a series of scientific characteristics that I ask of most any model system, or of any body of data which leads me to a conclusion, and this is all that I'm asking there.

Q. There also appears to be evidence that insofar as mesothelioma is concerned, crocidolite more often than chrysotile causes peritoneal mesothelioma. Is that a fair summary of the epidemiologic evidence?

A. Yes, I agree.

Q. Is that supportable in the biologic evidence? Is that consistent with the biologic evidence? Is that what you might expect?

A. No, please correct me if I'm wrong, but is there not also the data which suggests that peritoneal mesothelioma reflects a higher dose? Is that not what some of the people who have studied the disease say, that it represents a more intense exposure?

Again, we come back to the question of dose.

In other words, I have no...I fully accept what the epidemiologist says when he sees and reports the predominance of abdominal mesotheliomas. I have no quarrel with that observation at all.

Q. Is there...and you may have mentioned this this morning...but is there something in respect of the shape of the fiber that will more easily cause it to get to the peritoneal

Q. (cont'd.) area, than otherwise?

A. I don't know, because we are really not very sure how the material gets to the peritoneal area in the first place, and I think we would have to know that with some degree of certainty before we could postulate the second question that you asked about the shape of the fiber, its physical characteristics in general, I'm sure.

Q. There is also...and I'm sure you are aware of it...animal experimentation by means of inhalation and injection to determine the effect of different fiber types in animals, and particularly, as I understand it, by Dr. Wagner, which seems to indicate that you can inject chrysotile fibers, or have rats inhale chrysotile fibers that will produce mesothelioma at about the same rate as crocidolite fibers or amosite fibers. Fair?

A. Yes, sir.

Q. We have heard evidence that in respect of the chrysotile fibers, those are very thin fibers that have been specially produced to inject into animals.

A. I would have no quarrel accepting the fact that a very thin fiber, up to a point, in concert with everything we have said today, would fall into the pathogenic...

Q. And that's consistent with what you said that it's the thin fibers that are the ones we have to worry about?

A. Yes, sir.

Q. All right. If that's the case, if it's the thin fibers that we have to worry about, and if it is the case that in the workplace the thin fibers that you see more often are the amphiboles, rather than chrysotile, would it then be reasonable to expect that you would get a higher incidence of mesothelioma with amphiboles than chrysotile?

A. Yes, I would be prepared to accept entirely any data that is consistent with what you have just said, and that is independent of whether it's amphibole or chrysotile, its

A. (cont'd.) geometry, its dimensions, would be the major determinant. Yes, sir.

Q. All right.

In the workplace, as you actually find it, and maybe you can draw on your experience with your own company, can you give us any idea as to what you generally see as between the fiber dimensions of chrysotile on the one hand, and amphiboles on the other?

A. No, but I can provide it rather than...if I had known, I could have brought the information with me, but I certainly can provide the information to the extent that we have it, surely. I would be glad to do it.

Q. That information then, I take it, is available?

A. I don't know. If it is, to the extent which it is available, I really don't know. That is why I hesitate to state here, but you can be sure that whatever we have, in its entirety, we can make promptly available to you.

I suspect that prior to the concern over a distinction in biolocial effect between the various types of fibers, measurements were made of total fiber, without any concern over whether it was amphibole or chrysotile that was being measured, and clearly you would have to treat your membrane filter samples a little differently to distinguish between the two. It wouldn't be just a simple counting as is done for usual industrial hygiene purposes.

Q. Let me see if I can put what I am ultimately trying to get at in another way.

One of the explanations that has been put forward as to the different results that one apparently sees between Dr. McDonald's study on the one hand and Dr. Dement's on the other, is that in the textile industry the fibers tend to be worked more, handled more, therefore split apart more...I suppose more roughly approaching the kinds of hazardous dimensions that you mentioned this morning.

Q. (cont'd.) Would you agree with that?

A. That certainly is a possibility. It makes sense, certainly.

Q. One of the concerns that arises out of that is whether in fact, as the asbestos industry progresses from the 1950's, to the sixties, to the seventies, and so on, it is continuing or is using fibers in a way that are making them approach the kinds of hazardous dimensions that you mentioned this morning, and I suppose what I'm really trying to find out is whether there is any trend in the industry to use fibers in a way that makes them approach that kind of dangerous dimension?

A. No, a latter day equivalent of things like carding operations or something like that, really do not exist in activities that are primarily asbestos - reinforced cement or friction materials...at least speaking for the segment of the industry that I am involved with.

There isn't all that handling of materials or fibers put in, willowed, incorporated into plastics, incorporated into other mastics and so on. There really is no...at least in my limited circumference...equivalent of the old textile-type operation.

DR. DUPRE: Well, I think it's exactly on the point, counsel...

MR. LASKIN: Carry on, Mr. Chairman.

DR. DUPRE: ...let's put it in a slightly more specific way, Dr. Kotin.

Dr. Acheson, when he was here earlier this week, impressed upon us the importance of at least worrying about the possibility that chrysotile is now being milled in such a way that there is a tendency for a larger number of fibers in the most dimensions to be present, and he stated to us that, as I recall the testimony, that the Simpson Committee has had, itself, some concern about this. They were not, however, able to

DR. DUPRE: (cont'd.) get the kind of information that they would have liked to have. Of course, perhaps, simply because it is not available.

But specifically then, I guess the question I would ask you is whether you are aware of the extent to which chrysotile may, in recent years, have come to be milled in such a fashion that fiber configuration may have altered?

THE WITNESS: My hesitancy suggests that I am unaware of any major difference in milling operations within the recent past, but that isn't to say that it hasn't taken place.

I do know that by and large the greatest use for asbestos in asbestos cement relies more on its length in the classes of asbestos referred to, in addition to the numbers distributed - long fiber, long, high-grade fiber, short stubs and so on - so that at least in commerce the discussions and the descriptors are usually related to length rather than diameter. But that could only be a reflection of my ignorance, and I certainly am going to find out about that promptly.

I don't know that there is an equivalent to what Professor Acheson might have been concerned about, and if there is, then I think he sounds an appropriate note. He certainly does.

DR. DUPRE: I hope I didn't interrupt...

MR. LASKIN: No, that's fine. That's fine.

MR. LASKIN: Q. Just one or two more lines of questioning on fiber type. You dealt this morning with the whole question of the chemistry of the fibers, and to some extent, as I understood your evidence, it was that that did not play a role as far as you were aware, in its relative pathogenicity?

THE WITNESS: A. Well, to allow myself one bridge to crawl back, I think I said a dominant role or a significant role.

Q. Sorry. One of the pieces of evidence that we have had in the course of this inquiry is that when you are talking about making A-C pipe, which you just referred to to the chairman,

Q. (cont'd.) one of the ingredients in that pipe had to be an amphibole, and generally crocidolite, and as I understood the evidence, the reason for that was that it had some resistance to acid, where chrysotile did not.

Is that fair or unfair?

A. I believe that all that proves is that I can listen, not that I know. I have been told that as well, so I don't pretend that I know that firsthand.

Q. Is that..if that's a fair statement, is that statement consistent or inconsistent with your comment that chrysotile does not react to whatever acid environment there is in the body?

A. The concept of acid variability within the body is limited to decimals of alterations in PH...except for, let's say, the stomach where indeed you have a cement mixer, as it were, specifically constructed to handle low PH environments...but within the body a shift of PH beyond a fraction really represents a significant alteration in homeostatic equilibrium, and I just... well, the word is used the same, I don't think the context is the same in both.

But again, I am speaking more from the point of view of the biologist than anybody concerned with the recipes and techniques of production, because waters can differ much more significantly in their hydrogen iron concentration than tissue fluids can without wreaking any havoc.

Q. I am quickly getting out of my depth, Dr. Kotin...

A. No, no. I don't mean to make it sound any more complex, but clearly when you talk about acid-based balance in a living system, you are talking about very, very reasonably narror limits compared to the differences in the alkalinity and the acidity of water that one finds in natural sources.

DR. MUSTARD: Can I just...

MR. LASKIN: Yes.

DR. DUPRE: He's coming to your aid.

MR. LASKIN: I'm delighted. Just at the right time.

DR. MUSTARD: It is true, however, that the lysosomal enzymes, the enzymes in the cells, operate at an acid PH, some of them as low as a PH of four.

THE WITNESS: Four.

DR. MUSTARD: Secondly, it's also true, is it not, that your asbestos fiber is usually caught in a tissue reaction, an injury site, if I can use that term, and certainly in some tissue reactions it is known that the PH does drop in the tissue fluids, in an injury site. That is, you not only have the question of lysosomal enzyme PH dropping but you also have at an injury site a drop in PH?

THE WITNESS: Yes, depending upon, as I'm sure you will both agree, the primary cell of response - lymphoproteases as distinguished from leukoproteases, and the like, can have contrasting...but yes, the PH can vary in response to those injuries, certainly.

DR. MUSTARD: Would it not be reasonable, then, to suspect that in a situation in which the asbestos fibers are going to be exposed to lysosomal enzymes, either within a macrophage where they have been phagocytosed, or at a tissue injury site where you might get local PH changes, that if this susceptibility to an acidic environment is correct, that you might be able to demonstrate experimentally more rapid loss of chrysotile fibers?

THE WITNESS: Loss?

DR. MUSTARD: Disappearance of the fiber, yes. Theoretically you could at least do that experimentally. You could postulate it and try to test it, but has anybody ever actually tried to test it, that you are aware of?

THE WITNESS: I think Arthur Morgan is in the process of using his tag material for following the fate of the chrysotile fiber in different internal milieux. I am unaware of any data that are available now.

DR. MUSTARD: So at this time then, the possibility still would exist that under certain circumstances it might occur, but in effect there really isn't the evidence available from direct experimentation for or against the point. Is that a fair summary of the situation?

THE WITNESS: As you put it, yes. What I'm trying to think of is the contrasting internal milieux in which asbestos has been shown to have a biological effect, independent...in other words, I just don't have the data. I am not aware if the data are available.

But if it's going to produce a mesothelioma in the chest cavity, as distinguished from the pleural cavity or the visceral pleurae or the parietal pleurae, this all may be again, theoretically, yes, it's a possibility.

DR. MUSTARD: If I just take it a step further, since this is speculation in a rubber dinghy, you could argue that if the fiber gets into a macrophage and joins up with the lysosome, in our jargon the phagosome, that if the fiber is resistant to the acidic environment, then it will tend to persist in that macrophage, whereas if it is affected by the acidic environment, it will be lost, could lead over the long term to a different kind of outcome in the two circumstances.

I realize we don't have the answer to the question, but it is certainly testable with modern techniques and it would seem to me it would have to remain as a possibility under the circumstances, unless there is evidence to the contrary.

THE WITNESS: I have no quarrel with what you say.

MR. LASKIN: Q. Do I take it from what we have been discussing on fiber type that your judgement is that the one ingredient missing to come to some real conclusion on this question

Q. (cont'd.) is the measurement of dose and the testing of the different fibers at the same dose?

THE WITNESS: A. Yes.

Q. Again, accepting that there were no dose measurements, do we gain any assistance from looking at the neighborhood effects in terms of mesothelioma, between different mining areas? I'm here thinking of the South African mining area on the one hand, and Quebec on the other.

Because although there were no dose measurements, they were nonoccupational settings, but in the areas of asbestos mining operations.

A. It seems the unspoken preamble or suffix to your sentence is that these nonoccupational exposures are, as a corollary, lower dose exposure levels. Do I understand you correctly?

I don't want to put...

Q. Well, let's start with that. Let's assume that.

A. Yes, well I would submit there is very little evidence for this, and despite great importuning of people with household or neighborhood case information to get some dose studies, the data are not available. So it's really an unanswered question.

I would submit that by definition neighborhood cases are not inevitably low-dose cases. They could be, but again, the reality of the neighborhood cases is not at issue. The reality of the family cases is not at issue.

The reality of what constitutes the dose of exposure, I think is. Again, as has been said several times today, these are data that require just doing it or having the work done. No, I am not swayed by the fact that there are neighborhood cases of mesothelioma in South Africa. Not exonerating crocidolite, certainly not, but not providing the

A. (cont'd.) clincher, the proof positive that it is a more pathogenic form of asbestos than perhaps the non-amphibole.

Q. Do you make the same judgement about the gas mask worker studies, both in England and in Canada?

A. This is perhaps the one area that is making me hedge a little, although again with...the gas mask studies would be entirely convincing and the last thirty minutes would have been unnecessary, were it not for Whitwell's studies which clearly showed some constant doses in the presence of mesothelioma in body burdens and related them to disease, as you recall.

Q. Could you, again...perhaps for my benefit and my benefit alone...but could you explain what you mean by body burdens?

A. It is a concentration of fibers in target tissues, where disease has...is or is not...in an appropriately-controlled study...which means those exposed occupationally, those are appropriately controlled; in terms of paraoccupational exposure to get your neighborhood cases in; general population to get yet a third variable in, and then if that's going to be one axis on your grid, the other axis on your grid would be the occurrence, the rate, prevalence, incidence, whatever you have the date for, of disease, and see what correlations there are between exposure, disease and actual presence of fibers in the target tissue, and what we are speaking about, the lung, or the mesothelial surfaces.

Q. What does Dr. Whitwell's work in that area tell us about this question?

A. I think one...and again, he is the first to emphasize the very limited nature and the very small size of the study he has done...but I think, and if there were a copy around I would like to read it, but I think he makes the point that he

A. (cont'd.) correlates the presence of disease more with fibers per unit weight of lung than he does with exposure and with history, as I recall.

MR. LASKIN: Go ahead.

DR. DUPRE: I don't recall ever hearing about the study you have referred to. Is that Whidwell...?

THE WITNESS: Whitwell.

DR. DUPRE: Whitwell. W H I T...

THE WITNESS: W E L L, and it's in the January, I think, 1978 issue of Thorax.

MR. WARREN: Would it be useful if we tried to obtain a copy of that and make it an exhibit at this juncture, so that...

We have it, I'm sure. Do I have it with me? The answer is probably no...unless Dr. Kotin does.

MR. LASKIN: Is it amongst the many documents?

MR. WARREN: No, I don't think so.

DR. DUPRE: We certainly will appreciate having it.

MR. WARREN: Why don't we just note on the record at this time that we will obtain it, and then put it in as a sequentially-numbered exhibit at that point.

DR. DUPRE: Thank you, Mr. Warren.

DR. UFFEN: Having had this little interruption...

MR. LASKIN: Go ahead.

DR. UFFEN: ...are these body burden measurements made on live patients?

THE WITNESS: No, no. They are ashed lung from surgical specimens or autopsy specimens.

DR. UFFEN: You don't shove something down, take a little piece out?

THE WITNESS: No. It would be nice if we could do that, sir, but we can't because basically putting something down

THE WITNESS: (cont'd.) would only keep you in the bore of the tracheobronchial tree. It wouldn't get into the actual substance of the lung where the fibers are.

MR. LASKIN: Q. Do I take it that that study that you just referred to by Dr. Whitwell is the one piece of evidence, so far, that you are aware of which causes you perhaps to doubt what the gas mask worker studies would seem to indicate?

THE WITNESS: A. Doubt...it requires further elaboration. I'm not doubting. What...I guess what I'm saying is that there seems to be a way to get data that I would dearly like to have.

May I make an aside? Is there not a reference to the Whitwell work in the Simpson Report?

MR. WARREN: I'm sure there is.

DR. MUSTARD: There is a reference to it in the 1974 article in the British Journal of Industrial Medicine.

THE WITNESS: No, there was a recent article which was the lead article in Thorax. I think it was January, 1978, but we can get it.

I'm sorry. I didn't mean to interrupt you. I apologize.

MR. LASKIN: No, that's fine. I'll have Miss Kahn look for it.

THE WITNESS: I apologize, Mr. Laskin.

MR. LASKIN: No, that's fine, Dr. Kotin.

THE WITNESS: You are the ones to ask the questions, not me.

MR. LASKIN: Q. Just a general question, I suppose, to wrap it up, and I think I know the answer, but I'll ask the question.

On what ...on the basis of the evidence we do have to date, and what we know to date, is it your judgement that we should treat these different fibers differently or the

Q. (cont'd.) same for the purpose of establishing control limits for public policy purposes?

THE WITNESS: A. Working on the assumption that effective control will control all fibers, I think that a single standard probably would have to be my answer in terms of the positions I have taken on the questions that were asked before.

MR. LASKIN: Go ahead. I'm going to get to that.

DR. UFFEN: May I ask a question here?

MR. LASKIN: Sure.

DR. UFFEN: You gave us a magnificent lesson in basic biology, and I had hoped at the time that you would go one step further and explain to us the relationship in terms of your diagram and your understanding of the concept of a threshold, or whether there is, to use your own language, a no-effect level.

It seemed to me we were within an ace of having some understanding. Could you do that?

THE WITNESS: Yes, but...I believe that for carcinogens...well, to begin with, carcinogenesis is a stepwise progression of change from a normal cell to a population of cells that we call cancer...that there are two separate sequences of events, one that must in some way or another affect the genetic materials, the DNA, so as to produce an inheritable change in the cell. The other is a set of influences that take this cell and provide it with the necessary stimuli to go on and become a cancer.

So there are various names, different names for the two stages: One is initiation, and that would be the stage where we get involved with the DNA, where a molecule of a chemical compound or an atom of an elemental substance reacts with one of the chemicals in the DNA to alter it so that it gets the title of a transformed cell. A transformed cell is a cell in which a chemical agent has reacted with the DNA to transform it from its normal state to some other state.

THE WITNESS: (cont'd.) Now trivially, transformed cells are referred to as cancer cells. That's not so. A cancer, for one thing, is a cell, a population of cells, that have very, very distinct characteristics.

A transformed cell is just a cell that has altered DNA.

Well, once that takes place...this can take place at a level which will inevitably lead to cancer, likely lead to cancer or not lead to cancer, and this can be precisely quantified in the laboratory.

I can take a carcinogen like benzpyrene, or I can take a carcinogen like an aromatic amine or an azo dye or an F oxide, and give it at a dose level where you not only will get cancer, but we can predictably say I am giving this group of animals a hundred and eighty day fifty percent tumor dose, and be right within acceptable statistical variations.

I can also give a dose which says I am going to give a dose of a carcinogen which will produce a cancer provided enough animals live beyond thirty-six months of age.

Then I can give a dose of a carcinogen which says no matter how long the animals live, and more than that you are not going to shorten their lifespan by the carcinogen you give them, and never get a cancer.

DR. UFFEN: What about a solid carcinogenesis? You made a distinction this morning between the..

THE WITNESS: Yes, there are solid state carcinogens which, under certain circumstances, will give you, again, a predictable tumor rate. And under certain circumstances, only with minor alteration of the physics of the particle...in other words, its dimensions...you eliminate carcinogenicity.

So that again, there is a predictable rate for induction of cancers with certain solid state materials, and there is a way of modifying it to eliminate carcinogenesis. Do I make myself clear?

DR. UFFEN: I think I have it.

THE WITNESS: All right.

So now, the question then is, is there a threshold...and this is why the word threshold is perhaps in addition to being an incendiary word in the eyes of many...is perhaps a bad word, and I defer to nobody on how much I have misused it all my life. I don't say how you can say there is a threshold for the action of a molecule of an F oxide to react with one of the chemicals of the DNA chain, because one molecule reacting with one locus producing some covalent binding can do that.

But what is necessary for the production of the cancer undergoes a series of thresholds in each successive step, where you can...first of all, the carcinogen itself. I would submit that if you give a mouse or a rat, a dog or a monkey, a level of a carcinogen that produces no effect, I don't know whether you've had a threshold or not, but you've produced a no-adverse-effect level, and we all live with no-adverse-effect levels, and you can, in a very mundane way demonstrate it: The selfsame chemical carcinogens that are responsible for the increased risk to lung cancer in coke oven workers in steel mills, are the selfsame chemicals spewing out of every vehicle on every street in Toronto now and since the days of the internal combustion engine.

Now, it's almost...it sounds trivial, the analogy, but basically the carcinogenic polycyclic hydrocarbons are present in both situations, the promoting agents are present in both situations, and yet the coke oven worker is at an increased risk for lung cancer. The average urban resident isn't...

DR. UFFEN: If I look a little puzzled, my mind is coming along a sentence or two behind you all the time, and I'm trying to relate this to this solid carcinogenesis, where if my memory is right, it was the solid material that caused the enzyme to do something and get into the cell. Am I losing track, or have I got that right?

THE WITNESS: Well, the liberation of enzymes is associated with the preparation for the cancer, but not the actual change of a normal cell to a cancer cell.

DR. UFFEN: Then have I gathered from this correctly that the no-effect level, or sometimes called the threshold, is related to the process that goes on in altering the DNA, but not in this other process of the macrophages and the little primitive cells you talked about?

THE WITNESS: Exactly.

DR. UFFEN: Is that a well-established theory, or are we speculating?

THE WITNESS: To break it up into its parts, I think there is universal agreement that a macrophage has enzymes capable of digesting protein, capable of having these enzymes absorbed into other cells, capable of destroying tissue replaced by scar tissue, and stimulation of fibroblasts to make scar tissue.

I don't think there is any speculation associated with the fact that there has to be some form of interaction between an agent that we call a carcinogen, and a genetic material. There may be big arguments as to what it is, what the chemical reaction is, but it can be stated without any controversy that the genetic material has to be affected in some way because what you have in a group of cancer cells is an inheritable defect, and therefore it has to be inheritable in terms of an alteration in the genetic material.

So that, I don't think, is controversial.

I think what is controversial is whether in fact there are levels of exposure to a carcinogen which will not result in the development of a cancer in the animal model...it can be anything from man to a laboratory mouse...or that there are levels of exposure which are sufficiently low so that even though the initial interaction has taken place, they are capable

THE WITNESS: (cont'd.) of being repaired by a series of repair mechanisms available to the genetic material, or are capable being reversed because the effect is so minimal that it is transitory, it is labile, to the extent where it will not survive over repeated replications.

This, I think, is where we get into the area of controversy.

DR. UFFEN: I think we have progressed beyond biology 101.

DR. MUSTARD: I would like to go into the controversy.

It seems to me, Dr. Kotin, if one goes to this problem when it first emerged in relation to radiation, and if we were having this hearing in 1942...or let us say 1946...we could have been having a similar kind of discussion, and part of the problem was that there is biological variation - that not all people respond the same way to a standard stimulus.

The radiation story, as I recall, that it took Bentley Glass and fruit flies to really take the challenge, because the problem was how to expose enough biological material with variations, to trace doses to see if in effect there are some susceptible people who are going to be affected by the variations, and indeed he did find in the famous fruit fly experiment with radiation, that you could produce genetic damage within that process.

It seemed to me the problem with the asbestos story, even the animal experiments, is that nobody really has the megabucks to do the large number of animals that would be required to really take account of the biological variation question, to sort out the relationship, when all the epidemiological data shows that the extrapolation back to that soft point of the data suggests that there is a linear relationship and no threshold, which of course is supposition and you can shape all

DR. MUSTARD: (cont'd.) kinds of curves if you want to, as we've done at this hearing.

But the critical biological experiment, unless I have missed something, has not been done. That is, you take a huge cohort of animals and simply expose them to greater doses and see what happens...sort of to do the Bentley Glass fruit fly experiment, which I don't suppose anybody could afford to do.

That hasn't been done, has it?

THE WITNESS: No, but perhaps you don't have to, if I may...

DR. MUSTARD: All right.

THE WITNESS: ...with some degree of trepidation, suggest.

You see, in carcinogenesis we have the benefit of not an intimate number, but of many, many highly-inbred species where predictably we know what the spontaneous...for whatever euphemism for ignorance that might be...what the spontanous tumor incidence is.

Secondly, we have a marker that is unlike the almost untamperable reflection of a mutation, and that is the dose at which you can enhance or minimize the effect of the carcinogen by giving it at a noncancer-producing level for the lifetime of the animal...let's avoid the term threshold... then we can begin to study what is reversible or what isn't reversible by the judicious use of promoting agents....not only in terms of promoting agent potency, but in terms of temporal effects, altering the interval between the time of the initiator and the time of the promoter, altering the dose of the promoter, taking the initiator, giving the promoter also at a level which will not summate to a cancer in terms of a normal lifespan, letting a little time go and then promote again and see whether that promoting capability has been retained, or do you have to give as much promoter as you would have given assuming you hadn't

THE WITNESS: (cont'd.) given your antecedent series of promoters.

Well, this has been done to a faretheewell, and I think what it shows is that you cannot reverse, except perhaps by repair, you've got a DNA enzyme repair...an alkylated base.

But you can revert, dissipate, dilute out the effect of promoting agents. You can enhance the effect of a carcinogen by the temporal relationship.

Without going into it, what I'm trying to say is, we may not have to do that because we've got a clean end point... the cancer...one that is, unlike the mutation in the Drosophila, really gives no evidence of its presence until just before you may get to see the proliferative phase. You can paint a thousand or a million mice with a known carcinogen, and if it's a polycyclic aromatic hydrocarbon, three weeks after you do that you have no way of identifying which population of cells have gotten that polycyte, although residual fluorescence may exist in the area.

But you have no way of identifying...we don't have that marker, and one of the reasons I don't think we have that marker is...and this is purely speculative on my part...is that we don't have an indelible lesion yet...not in terms of the original alkylating of the base, but in terms of the progression to cancer.

DR. MUSTARD: Have the animal experiments been done with asbestos, along the lines you are suggesting, or are those the things that need to be done?

THE WITNESS: That's what we have just about convinced Professor Brand.

DR. MUSTARD: But they have not been done?

THE WITNESS: They have not been done, because basically it is a difficult one in the sense that you, unlike with a chemical where you can follow either with metabolites, or you can label it, but now Professor Brand, who is really the

THE WITNESS: (cont'd.) high priest of solid state carcinogenesis...it's an area that has fallen in low esteem until now that asbestos, I think, is being recognized and accepted as a solid state carcinogen...so I certainly agree, and I thought you were going to say, which I would again have to accept, that the effect of a linear track change, an ionization track, cannot be diluted out - it's there.

But we don't necessarily see the same thing with carcinogens at very, very, very, very low doses, and that is why you will find in the real sophisticates in the field of carcinogenesis...I'm talking about the Van Prato's and the Henry Pethos...they will unconsciously lapse into noncarcinogenic.. or Manny Farber down the street here at the university...will lapse into noncarcinogenic dose, subthreshold dose and so on.

I think Farber perhaps has contributed as much as any one man to the sequential steps in the evolution of a cancer from a transformed cell. The quarrel is not with the transformed cell. I think the quarrel is with the equating of a transformed cell with a cancer.

I beg your pardon, I didn't mean to...so your point is exceedingly valid and I just think that there is a little more information than the greater variability in the area of carcinogenesis, which allows us to manipulate and study effects.

In fact at one time there was hearsay that even the initial DNA carcinogen interaction was reversible. It isn't reversible in the sense of reversible. It may be reversible in the sense that along can come a nuclease and chop it out and then restore the integrity of the DNA molecule.

Sorry.

MR. LASKIN: It's okay.

MR. LASKIN: Q. Let me see if I can deal with this whole issue that we are discussing.

As I read your articles, you set out four factors

Q. (cont'd.) or four aspects of response that characterized exposure to asbestos, of which the one that we have just been talking about was one of them.

As I apprehend it, if the one factor was the latency period...and I take it there is no real controversy amongst the scientific community about that fact?

THE WITNESS: A. I don't know of any.

Q. And the second factor was the dose-response relationship?

A. Yes, sir.

Q. Do I take it that there is no real quarrel in the scientific community about that response?

A. Again, to be, I think, precise, there are some people who are questioning a dose response, the presence of data to warrant a dose-response conclusion for mesothelioma. You are aware of that. It may even be a supposition that might have been articulated at these hearings.

I think it's important to recognize that there are some people that question whether the data support a dose response.

I believe there is a dose response. Heaven knows if you asked me to go and put the points on the dose response, I would just put at one end 'general population', and at the other end, if you will, the 'crocidolite miners' in the Northwest Cape, and say the points are somewhere between those, because with mesothelioma we do have a marker tumor, and certainly in the last...since 1964, let's say, the New York Academy of Sciences... and that's a decade and a half. Clearly any increase in the general population would not require monumental amounts, and more than that it is a tumor that probably would not have been masked by other tumors.

Like, you would have to have a pretty potent influence for lung cancer to become overt in the presence of the

A. (cont'd.) overwhelming role of cigarette smoking.

So, anyway, yes. Dose response, I think, is, at least for me, a position that I can live with and do live with.

Q. Just to pick up a point which you mentioned at the end, you would agree that there is no relationship between cigarette smoking and mesothelioma?

A. I am unaware of any.

Q. Can you just elaborate a little bit about what you mean when you say mesothelioma is a marker disease?

A. Well, it's an unusual tumor in the sense that it is a neoplasm that is sufficiently uncommon...rare if you will, in the nonexposed, that any cluster of cases in a nonexposed group...and we could all night argue what exposure is...but anyway, what I think would be identifying, no less than in an exposed group like the vinyl chloride monomer workers, angiosarcoma was a sufficiently rare tumor that it really took little more than a handful of cases to document a cause-and-effect relationship.

So this is what I mean by a marker tumor. A marker tumor would be, a good example would be the thyroid cancer in children who were given radiation treatment for thymic enlargement. Thyroid tumors are not all that common, and it isn't likely to be masked except maybe in a high goiter endemic area or something like that.

Q. I suppose the other side of that is that you can more readily determine what has caused those tumors. If it's not masked on the one hand by something else, then you can more quickly go to the essential cause?

A. Yes. Well, at least you can characterize the populations that have the increased risk....first make sure they have it.

Q. We've dealt with dose response. The third

Q. (cont'd.) factor you mentioned was multifactor etiology in relation to some diseases, and you mentioned smoking...

A. And lung cancer.

Q. And lung cancer. And I take it there is really no controversy in the scientific community about that interaction?

A. No, I think...but here again, in fairness, one has to state there is great controversy as to which is the determinant and which is the modifier, and so on, that there are differences there. But I don't think anybody questions the joint effects, the cofactorial effect.

Q. Then the fourth factor is the factor we started out with when Dr. Uffen raised his question, which was the no-effect level...

A. No-effect level.

Q. ...and that, I take it, is the response which you say there is some controversy about?

A. Even more, I would have to emphasize that I am in the minority, to be perfectly candid, in terms of workers in the field.

Q. Even taking your position at an individual level, do I understand your response to one of Dr. Mustard's questions, or in any event in his question, that that no-effect level at an individual level can vary depending upon individual susceptibility?

A. Individual susceptibility is a determinant in all epidemiological studies and in all biological systems, and that is why in attempts to study mechanisms you try to reduce variability.

This was the genesis, really, of inbreeding of animals, beginning up at the Jackson Laboratories in Bar Harbour, Maine, was to provide inbred strains for studying those things where individual susceptibility was reduced to an irreducible minimum..it's still there, but in these...

Q. If you take your response at a no-effect level, and you translate it into a population of employees, does it mean that if you are going to draw some dose-response relationship for that cohort of employees that you would not draw the relationship through the zero intercept on the Y axis?

A. Well, let me first back up a little and say...the question which is, I think,...may I ask...and that is... I wouldn't draw any line. Let me answer your question first.

But it's all very well for me to say here intellectually that I believe there is a no-adverse-effect level, and then the question that my former associate Yulla Bingham asked me, that's great, Paul, you've finally convinced me there is a no-adverse-effect level...tell my how, libel deleted, I can use that as a regulatory. And that's an entirely problem.

Here I think you use it on the basis of what data you do have, what population data you have. You have...and it's different because there are two universes in the world of regulation: One in which you want to introduce an agent into the environment, and one where there is an agent in the environment - either part of our natural world or it has a...and for that, I think, is where you may use that as the total body of information, and if you can see in a population a response to reduced levels of exposure, if you can see a response to control efforts, then I think you can derive comfort from the fact that you can establish a regulatory posture and at the same time, from my point of view, not fly in the face of biological principle.

Do I make myself clear? Not really, eh?

MR. LASKIN: Not entirely.

THE WITNESS: What I'm trying to say is, that basically saying that there is a no-adverse-effect level is of very little help to a regulator who has got to decide that a new product called fluid extract of popcorn is going to be put on the market. But I submit it's a different universe where you

THE WITNESS: (cont'd.) have an agent for which there are epidemiological or occupational studies which show what the experience of workers has been over a period of time.

MR. LASKIN: Q. Since that is, I take it, the case with asbestos, how then does your criteria or your response at a no-effect level help in terms of regulation, in that sense?

THE WITNESS: A. By and large, you look at populations, see what the prevalence or incidence of disease is, have an idea of what they were exposed to, and draw some operational conclusions.

Q. And...

A. And you use data of the McDonalds of the world or Selikoffs of the world, and come to a position.

Q. In coming to that position, is it legitimate, in your judgement, to take the data that you have and extrapolate it to some extent?

A. I don't think you can generalize, certain data you can extrapolate on.

I'm not sure I understand your question, I'm sorry.

Q. How...let's be specific, let's take Dr. McDonald's data and let's take whoever else's data you would like to include...how do you use that data?

A. You use it to the extent the data are available, you look at prevalence, incidence of disease as related to exposure levels, again coming back to the drum I seem to be beating all afternoon, and that is body burden.

You see, the problem with asbestos is not that it's unique in terms of the principles involved, it's unique in the fact that we have no expiratory product that is a marker, or a reflection, of the presence of asbestos in the body.

If it's arsenic or a series of aromatic amines or azo dyes, a urinary excretion profile will give you some index or some...some index of exposure. We don't have that kind of a

A. (cont'd.) marker and this is why we have to resort to the very cumbersome business of, let's say, body burdens if we are going to elucidate some principles that are dose response.

Q. Let me put to you my problem, and you respond to it.

As I understand what...and you have admitted you are perhaps in the minority in this no-effect level position...as I understand what the majority of people would say, it's that admittedly we don't have any measurements in most cases, and probably in all cases down at those low levels of exposure, but if in fact you draw a linear line, a line that's linear, and you draw it down to zero, that's of assistance in terms of regulation-setting mechanisms. It's a simple matter to work with, you can extrapolate along that line, and from a public policy point of view, I take it, you are being somewhat prudent because you are probably overestimating whatever risk there may be.

Now, are you...the answers that you have just given me before, are you suggesting that that is or isn't a sensible approach with a substance that's already in the environment, that we already have with us?

A. Again...I don't mean to be a copout...public policy at best is a difficult thing...

Q. Agreed.

A. ...and as an alien in your country it's even hazardous to a greater degree.

No, I'm entitled to my opinions about public policy as a citizen, not as a scientist , and so on.

So, no, I would say you have to use the data you have available, and I think that the data that you have available will give you the basis for a matter of public policy. A matter of public policy is allowing to use carcinogenic chemicals for the treatment of metastatic cancer, and you just hope that the

A. (cont'd.) patient lives long enough to get the cancer from the carcinogenic agent, which happens to be a therapeutic agent at the same time.

I mean, that's farfetched, but I think, I guess it's a matter of weighing all of the elements in public policy.

I think what I would say is that asbestos in common with virtually all environmental agents...and I think that this probably cannot be stated too frequently...is, at certain levels, capable of being hazardous and inducing disease, and in fact has done so. I am equally convinced that there are levels of exposure which, for the working lifetime or for the residence time of any person, there are levels of exposure compatible with the material in commerce that will produce no adverse effects... no measurable adverse effect...by the standard rubrics we use for measuring adverse effects.

Q. To take your point, what epidemiological evidence is there that would support that proposition?

A. Despite the very selfsame article that Dr. McDonald, for instance, said he believes he is most comfortable extrapolating back to zero, he has clearly demonstrated a level at which he could demonstrate no adverse effect...in the article.

Q. For which asbestos-related diseases?

A. I think he was talking about lung cancer and asbestosis, and as you pointed out, he had so few mesos that that was really incapable of being...the most recent followup on his population of miners and millers in the Province of Quebec.

Q. Is there, from your review of the literature, any other epidemiological studies which would support your proposition?

A. Yes. This isn't to say that there has been no disease. I think that one can look at trends in other articles...I suspect some of Rubino's studies where indeed Rubino reports the presence of disease in Italy, has showed a

A. (cont'd.) decline associated with control efforts. I think we at J-M have some data on a couple of our facilities which suggest that control efforts in plants that were built, our most recent plants, would show a...using asbestosis only...that's the only thing where we have done prevalence and incidence studies...which show curves that suggest that we are at a no-adverse-effect level.

So there are enough at least, I think, to make the position a tenable one.

Q. Would you also agree that there are other studies which are at least consistent with the opposite conclusion?

A. Oh, I surely would.

Q. Which studies would you include in that category?

A. Again, the studies I would include is where the author states his position. I'm not sure that I'm aware of any data. If you look at the studies coming from Mount Sinai, they really have no measurements of their exposure of their insulation workers in early days. They state so in so many words, where they are now seeing the latent period manifestation of diseases.

I guess I could go through a bibliography and tick off those which I think would perhaps arrive at different conclusions, but the important thing, I think, is that by and large...and Dr. McDonald is an excellent case in point.. where he is satisfied that his data...unless I don't read his data correctly, and don't let me put words in his mouth...I read his data as saying that there is a no-adverse-effect level in the population that he is studying. It's a large population, it has been followed for a long time, and I'm really prepared to say that that's very, very convincing.

So I just am hard put off the top of my head to tick off the other articles that would take a position contrary

A. (cont'd.) to my own, other than to say that certainly I read enough that..

Q. Let me in fairness to...

MR. WARREN: John, I just wonder how much longer we have, because I know he has got an appointment.

THE WITNESS: We'll knock off pretty soon. I'm getting bushed, too.

MR. LASKIN: You say whenever you want, but let me in fairness to Dr. McDonald put to you what I understood to be his position as he stated it before this inquiry, because it really gets to an issue I wanted to ask you about, and the record will certainly correct me if I'm wrong, but as I understood his position, he did not say there was a no-adverse-effect level or no excess risk level, but what he said was that epidemiological tools weren't sufficiently precise enough to be able to measure it.

THE WITNESS: A. At the risk of being an inhospitable guest in your country, that's just so much gibberish, that statement. It doesn't mean anything. Because basically one can say that about anything and everything. It's a tool that has been valid enough...and I don't mean just Dr. McDonald is wrong... but I mean basically, sure, there's always the possibility that the method that we are using is insensitive to describe an effect, and I think that's an unspoken caveat to all of our data.

When I refer to the dose that would give one thousand or ten thousand mice who lived their lifespan, no dose of cancer, the unspoken caveat was that if there had been twenty thousand, maybe there might have been one cancer, even though they are highly-inbred C57 black or A or C3A, it makes no difference.

No, I don't think that adds substantively to the problem, and I wasn't putting words in Dr. McDonald's mouth. What I was doing, as...I was concluding from his data what I saw

A. (cont'd.) in them, that's all.

Q. But to take your example, it may be the case because of a particular population you have chosen, because the excess risk may be small, that you may not have selected the population which has the excess number of deaths, or whatever index it may be?

A. No question. That's a possibility. You may be right.

DR. MUSTARD: I was going to say, maybe we should take a look at what McDonald actually said and come back to it at some time.

I mean, I have my recollection of what he said, but it's late in the evening and I'm hypoglycemic.

THE WITNESS: Yes. Thank you.

DR. DUPRE: Dr. Kotin, could I, if I might, just ask a question that arises directly out of your dialogue in the last five minutes with Mr. Laskin, in case I lose it?

As I take it, you say that you have studied some plants at this point which would appear to confirm the hypothesis of a no-adverse-effect. How long have these plants that have been studied been in existence?

THE WITNESS: Over twenty-one years, Dr. Chase? Excuse me? How long have the plants been in existence?

DR. CHASE: Twenty to twenty-one years.

THE WITNESS: Twenty to twenty-one years.

DR. DUPRE: I asked...that certainly is consistent with your tab six, which is your testimony at the House of Representatives, where the plant that was mentioned was one that had been around twenty-two years.

THE WITNESS: Yes.

DR. DUPRE: The point that is then made in that testimony is, of course, as you point out, you pointed out here, there is no evidence at this juncture of asbestos-related disease.

DR. DUPRE: (contd.) There are, however, some cases where there are pleural changes indicating exposure.

THE WITNESS: Unquestionably.

DR. DUPRE: Now I am just wondering if, as a layman, you can help me out at this point.

Is it possible that when you are looking at a plant that has been around twenty-five years, let's say, if the kind of finding that you have made is in front of you, you could easily perhaps simply entertain, instead of a no-adverse-effect situation, the possibility that what you are looking at here is the normal dose-response situation.

A plant that has been around for twenty-five years probably deprives you of doses sufficiently large that a response would have materialized, which is not to say that a response couldn't materialize, say, at year thirty or year thirty-five.

THE WITNESS: I think I say in the selfsame testimony that one would...let me make two comments: One, I think the pleural changes are just that - changes. They are not disease and not necessarily the hallmarks, I think, of impending disease.

Again, I think that's an area of controversy, but here I suspect I'm not in minority.

Now as far as dose response resulting in a case twenty-five years from now, thirty years from now, I certainly recognize that. In fact, I think in my testimony I say, or should have said, that the possibility of such a case arising does have to be considered. But it in no way gainsays the beneficial impact, although that's the wrong word, I don't mean beneficial impact... the biological impact of reduced exposure. You have to allow for that contingency in any biological system.

DR. DUPRE: Thank you for allowing me to slip that in.

MR. LASKIN: Q. Are those...the studies that we

MR. LASKIN: Q. (cont'd.) have just been discussing, are those the morbidity studies that you referred to as being almost complete when you spoke to us in our informal public meetings last fall?

THE WITNESS: A. Yes. I think they are complete.

Q. They are complete now?

A. I think so.

Are they complete, Dr. Chase?

DR. CHASE: That phase of them.

THE WITNESS: Yes.

MR. LASKIN: Q. Are we at some stage going to have the benefit of those studies and that evidence before this Commission?

THE WITNESS: A. Yes, sure.

Q. Okay.

A. Affirmative.

Q. I take it that's when Dr. Chase is going to testify before us?

A. I don't think Dr. Chase is going to testify, but we can make submissions to the Commission, of course.

MR. WARREN: John, just to add...I'm frankly, I think everybody is saying that those data are going to be put before you, but I don't want to leave the room with any implication that Dr. Kotin or I, or Dr. Chase, know the answer to that question.

Probably my colleagues do, but I don't, and I don't want to mislead anybody.

THE WITNESS: No, no. Dr. Chase will be the one who determines when the data are...

MR. WARREN: The question is when the work can be done to get things together to get them for you, rather than...

DR. DUPRE: Now, I'm going to suggest, class, first of all, that we are in trouble. Dr. Kotin has had a very long day and the air conditioning, on top of that, has now been turned off

DR. DUPRE: (cont'd.) for about half an hour.

We have Dr. Gibbs coming tomorrow, which means at this point we are groaning under the weight of our visiting professors, and at the same time we do not wish to sacrifice our educations unduly.

Now, I have ascertained that Dr. Kotin is very much of an early bird. That, of course, I think goes for the people at this table.

Is there any problem with our reporter in the early hours of the morning?

THE REPORTER: How early?

DR. DUPRE: Let's say eight o'clock?

THE REPORTER: I was thinking of real early, but no problem there.

DR. DUPRE: All right. Well, I think that that would indicate then, that we should now rise, but in the tradition of some of the very old liberal arts colleges that I once knew a couple of decades ago, reconvene for class at eight a.m. tomorrow morning, and we can then assume that we will have the benefit of Dr. Kotin's instructions for the rest of the morning.

Perhaps before counsel disperse, you might, counsel, speak to your other colleagues so that you can give me an appropriate batting order when the time comes.

Mr. McNamee?

MR. McNAMEE: Yes, Mr. Chairman, I've already done that and I understand that I'll be...I think I'll be half an hour and Linda has indicated she will be an hour or more, and...who else is going to be on?

MISS JOLLEY: Sorry, the Injured Workers are going to be on...

MR. McNAMEE: ...for half an hour, and I don't know about Mr. Starkman. He might be half an hour. How much longer do you have to speak?

MR. McNAMEE: (cont'd.) Of course you people will want another...

DR. DUPRE: There is the Commissioners' Hour.

MR. McNAMEE: So perhaps...we'll have to...eight o'clock is...

DR. DUPRE: We must, of course, have sufficient time to take advantage of Dr. Gibbs.

MR. McNAMEE: I was wondering, it wouldn't be against the Commission's policy if...I have two or three questions of a medical nature and if I indicated, is there anything wrong with indicating to counsel for Dr. Kotin the nature of the questions so that he can prepare himself, or is that...?

DR. DUPRE: May I simply leave it to you to sort out once the Commission has risen? I don't think we would have any rulings on that.

So we now rise until eight o'clock tomorrow morning.

THE INQUIRY ADJOURNED

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